Key Topics in Management of the Critically Ill

Marcela P. Vizcaychipi
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Editors

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ISBN 978-3-319-22376-6 ISBN 978-3-319-22377-3 (eBook)
DOI 10.1007/978-3-319-22377-3

Library of Congress Control Number: 2015954553

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Foreword

Intensive care medicine is a rapidly evolving specialty. In the last decade, there have been advances in technology, diagnostics, treatment and in our understanding of the pathogenesis of diseases that affect critically ill patients. Management of conditions such as burns, stroke, acute liver failure, thromboembolism and delirium have changed dramatically over the last few years with new diagnostic and therapeutic modalities. These topics are eloquently covered in the relevant chapters in *Key Topics in Management of the Critically Ill*.

Physical and neuropsychological rehabilitation after intensive care has been another area of specific interest to the intensive care community over the last few years and covered in the chapter on *Neuropsychological Rehabilitation for Critically Ill Patients*. Published literature report approximately 30 % of patients suffer from anxiety, 20 % of patients suffer from depression and up to 60 % of patients suffer from post-traumatic stress disorder after intensive care admission with the associated long-term socio-economic consequences. Whereas historically intensive care physicians were satisfied to leave follow-up care of these patients to the community, there is now increasing recognition that early intervention during and immediately after intensive care admission can positively impact on recovery, length of hospital stay and healthcare costs. In some countries, such as the United Kingdom, national guidance and policies have been developed to help address long-term physical and neuropsychological sequelae of critical illness.

The use of ultrasound and echocardiography are no longer limited to the remit of radiologists and cardiologists. The increased portability, usability, and advanced technology of modern ultrasound and echocardiography machines mean that ultrasound and echocardiography are now routinely used by the bedside to help direct clinical care in modern day intensive care units. Two chapters in this book are dedicated to the use of these important diagnostic modalities.

Finally, intensive care medicine is a multidisciplinary specialty that relies on effective teamwork, leadership, and communication to achieve best outcomes for patients. The chapter on *Simulation in Intensive Care* highlights how simulation can be used effectively to enhance technical and non-technical skills (human factors) such as team dynamics, decision-making and situation awareness to improve patient safety, patient outcome and staff satisfaction through interdisciplinary training.

Key Topics in Management of the Critically Ill offers a succinct guide to important topics in intensive care written by international experts in the field. The chapters are designed to provide a comprehensive summary of the pertinent clinical, diagnostic and management principles for the practising intensive care clinician.

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Simulation Training in the Intensive Care Unit

1

Alina Hua, Helen Williams, Naz Nordin, and Kevin Haire

1.1 Introduction

The dictionary definition of simulation is the technique of imitating the behaviour of a situation or process by means of a suitably analogous situation or apparatus, especially for the purpose of study or personnel training.

Medical simulation is now an accepted part of teaching and training in all forms of healthcare. Over the last 30 years, technological developments have led to a huge diversity of simulation modalities. These advances have coincided with an increasing awareness of patient safety issues and the adaption of risk management processes from industry. Many early simulation training modules were directly adapted from the aviation industry.

Anaesthetists were prominent in the early days of simulation-based training, and, in particular, the development of what is now known as 'Human Factors training'. In 1992, Dr. David Gaba (an anaesthetist and pilot) and his colleagues at The Palo Alto Veteran's Hospital published their landmark work using simulation-based training for anaesthetists in crisis resource management [1]. Over the next decade,

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_1

simulation centres appeared across the United Kingdom and Europe, delivering similar courses for anaesthetists.

Intensive care has more recently embraced simulation as a training modality. However, there is a wide variation in how this has been implemented.

1.2 Rationale for Using Simulation-Based Training in Intensive Care

Simulation training can be expensive in terms of equipment and personnel. What does simulation offer that other educational modalities do not?

The simulation setting:

- Is a safe environment where learning can take place without risk to a patient
- Is an experiential form of adult learning
- Provides training opportunities for individuals and teams
- Is flexible and adaptable to changing educational needs
- Allows trainees exposure to rare clinical scenarios
- Allows teams to work together in realistic situations and reflect on their performance
- Allows teams to practice delivering complex treatment algorithms in stressful situations
- Provides an environment for educational research
- Simulation as an educational process provides the opportunity for:
- Encouraging reflection
- Formative assessment, including debriefing and feedback
- Summative assessment

1.3 Best Practice in Delivering Simulation Training

The knowledge base in the use of simulation training is now significant. The evidence base for the appropriate use of simulation and its effectiveness is growing.

There have always been questions regarding the effective use of simulation-based and technology-based learning. When and where to use it? What form of simulation? How do we measure the effect of this training? Does the training translate into the 'real' clinical world? We now have a solid body of evidence available to begin to answer some of these questions. The extensive review by Issenberg et al. went as far as producing a best practice guide for simulation training [2]. The review compiled a list of essential features for any simulation training. The most important part of the process was deemed to be effective feedback facilitated by trained instructors. Most forms of simulation are part of an experiential learning process, where reflective learning is a key component. It is therefore important to understand that all forms of simulation must be part of a robust educational process, if they are to be effective. It is also crucial that the effectiveness of this form of training is evaluated.

How do we evaluate the outcomes of simulation training?

1.3.1 Outcome Measurement

The effectiveness of simulation training is assessed in the same way as any other educational module. The standard method is to use Kirkpatrick's four-level model for evaluating training [3].

Level One. Reaction.
Evaluation of the participants' satisfaction with a training intervention. This is usually measured using simple post-course feedback questionnaires.
Level Two. Knowledge acquisition.
Evaluation of the participants' change in knowledge, skills or attitudes. This is usually measured by some form of formal assessment, such as a post-course MCQ.
Level Three. Behaviour.
Evaluation of a change in the participants' behaviour in response to the training intervention. This is more difficult to measure and can require more complex questionnaires or formal work-based assessments.
Level Four. Patient outcome.
Evaluation of the effect of a training intervention on patient outcome. This can be very difficult to obtain and may require sophisticated reporting systems, such as critical incident reporting.

The evidence suggesting a positive effect from a training intervention increases as we move from Level 1 to 4. As the evidence level increases, however so does the difficulty and complexity of data collection.

In the early years of simulation training, most of the evidence related to educational outcomes was generally Levels 1 and 2. However, in more recent years, there has been a realisation of the importance of obtaining Levels 3 and 4 evidences. Simulation training often requires substantial resources, and it is vital that evidence is gathered to justify any training intervention of this sort. It is important that we insure that simulation training does translate into the 'real' clinical environment. In the future, a vital part of any project using simulation training must be a clear mechanism for evaluating the extent of this translation.

1.4 Classification

There is a wide range of terminology related to simulation in its different forms. A simple but comprehensive classification appears in the recent textbook *Essential Simulation in Clinical Education*. (Table 1.1) [4].

1.4.1 Part-Task Training

Part-task simulation training is the breaking down of a large, multicomponent task into simpler individualised elements. This type of training focuses on the specific

Table 1.1 A simple classification of simulators

	Appearance	Interaction with the learner	Educational context
Part-task trainer	Realistic, but of a single body part	Feels realistic, but limited or no response	Repetitive practice of isolated skill
Fully body simulator	Realistic body, often with associated physiological modelling	Allows examination (e.g. pulses) and realistic interactions	Realistic practice of whole scenarios
Screen simulator	2D image of patient, equipment, or staff	Realistic response to input via keyboard or mouse	Cognitive exploration of a variety of situations
Virtual reality	3D image of a patient, equipment, or staff	Realistic response to input via a variety of methods	Realistic practice, often of a defined task
Real people as simulators	Real people	Verbal and non-verbal communication	Practice of a variety of clinical skills
Hybrid simulation	Any combination of the above	Verbal and non-verbal communication and interaction	Realistic practice
Simulated environments	An entire clinical environment	Full interaction with patient and team	Realistic practice and team training

fundamentals of a task and the development of 'automated skills', which would otherwise be challenging to achieve in the context of a complex task. They are specifically designed to replicate only part of an actual clinical scenario [4]. Some simple examples include venupuncture, cannulation and suture pads. This type of training is now familiar to most healthcare professionals.

More complex part-task trainers are now commonplace in surgical training. There is substantial evidence available on how to incorporate these trainers into a wider training programme [5]. In particular, it is important that trainees experience part-task training at an appropriate point in their learning curve. Once a trainee has mastered the technical skill required, the part-task can be incorporated into a wider clinical scenario where other non-technical skills will be needed (Fig. 1.1).

There are now realistic part-task trainers for almost every practical procedure that occurs in Intensive Care. Realistic, airway and tracheostomy trainers are widely available [6]. The use of chest drain and central venous access trainers is now well established. The developing trend is to incorporate these trainers into specific learning modules that form part of a wider curriculum [7].

A typical modular approach to teaching chest drain insertion would begin with some screen-based material, outlining the anatomical, technical and equipment issues. The students would then progress to working through the procedure on a part-task trainer facilitated by an experienced practitioner. Once the students have reached an acceptable level, the part-task trainer can be inserted into a more complex simulated scenario. The students are then required to carry out the same technical task, but under time pressure and a certain level of stress. This stepwise fashion allows the skills learned to be gradually reinforced. At each stage, a formal feedback session is essential.

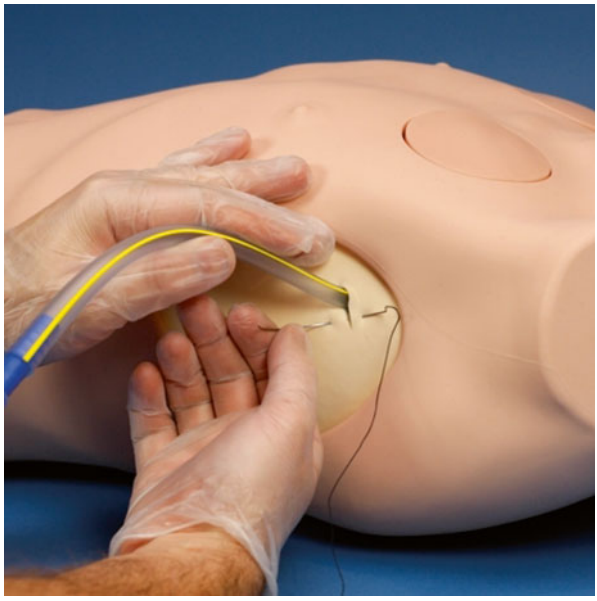

Fig. 1.1 Part-task trainer for chest drain insertion

The uniformity of part-task trainers to some degree allows a level of comparative assessment. This may be useful in monitoring the students' progress and detecting problems at an early stage.

1.4.2 High-Fidelity Simulation Training

High-fidelity or 'immersion' simulation incorporates knowledge, technical and procedural skills alongside non-technical skills such as communication and teamwork within realistic scenarios. The high-fidelity manikins give immediate, real-time feedback on the patients' condition and response to interventions. This dynamic component encourages the participants to become immersed in the scenario; so, their responses and behaviours become closely related to a 'real' situation. This dynamic component of high-fidelity simulation training has been shown to lead to increased confidence and decreased anxiety amongst the trainees. However, the key element is the debriefing session where participants partake in a detailed discussion of their experiences as a part of an experiential learning process. This process is most effective if carried out as a team exercise, with all those involved taking part. The validity of high-fidelity simulation training lies in careful planning, authenticity, close clinical resemblance and high clinical relevance (Fig. 1.2).

An example of high-fidelity simulation training in the Intensive Care Unit (ICU) setting was conducted in the University of Toronto where a new protocol for cardiac arrest in patients with severe acute respiratory syndrome (SARS) was evaluated. The simulation training raised issues that had previously not been considered, in particular the time taken to don the personal protection system (PPS) in an acute

Fig. 1.2 High-fidelity simulation team training

situation, techniques of defibrillation, and ergonomic factors such as minimising stethoscope use to avoid dislodging the PPS helmet. Effective changes were then made to improve the protocol [7]. High-fidelity simulation has been used effectively to familiarise ICU staff with new complex treatments, such as extracorporeal membrane oxygenation [8].

All ICUs will have critical incidents. High-fidelity simulation is an effective way of examining these incidents in a safe and positive environment leading to improvements in patient outcomes.

1.4.2.1 Non-technical Skills and Human Factors Training Using High-Fidelity Simulation

It is increasingly recognised that part-task training alone, whilst useful, cannot fully prepare a learner for working in a high-pressure environment. Working successfully in a busy, multidisciplinary clinical area such as the Intensive Care Unit requires a variety of 'non-technical skills', such as situational awareness, team working and communication. Within the aviation industry, focused training on these skills is routine and often referred to as 'Crew Resource Management'; within medicine, the terms 'Crisis Resource Management' (CRM) or 'Human Factors training' are more common [8].

Whilst it is relatively straightforward to design protocols to teach a practical skill, such as central line insertion, or a sequence of tasks such as an Advanced Life Support algorithm, an approach to teaching these 'soft skills' may be less readily apparent. High-fidelity simulation training is well placed to meet this need. In a high-fidelity situation, learners are exposed to a simulated clinical environment

that has been designed to be as realistic as possible. Manikins have evolved in complexity over the years to allow an increasing number of clinical scenarios to be played out, and it is now possible to simulate high-fidelity medical, surgical, anaesthetic, paediatric and obstetric cases. This requires dynamic interactions with a simulated whole patient, other members of a clinical team, a ward environment, medical equipment, and additional demands such as prioritisation and external communications.

The complex nature of these simulations makes them difficult to standardise and control; an effective post-simulation 'debriefing' is vital to ensure that learning opportunities are maximised. The debriefing process involves focused discussion with participants following the simulation to provide feedback on key skills, good performance and areas for improvement. Most feedback is formative rather than summative in nature, and various models and practices for delivering feedback exist, such as the four-step model by Rudolph et al. [9].

Effective communication within multidisciplinary teams is a key component of everyday practice in Intensive Care, and failure to accurately relay situational information or instructions is a common feature of critical incident analyses. Despite this, however, very little focus is given to multidisciplinary interaction in undergraduate or postgraduate medical education [9]. There is increasing evidence to support improvements in clinical team working and patient outcomes as a result of human factors targeted simulation training (Kirkpatrick's Level 3 and 4 outcomes). A review by Boet et al. identifies nine studies, which demonstrate improved performance in a number of situations such as trauma and paediatric multidisciplinary resuscitation teams, translating to improvements in clinical performance and patient outcomes [10]. Emerging studies suggest that this would be an acceptable and valuable training method in the Intensive Care environment [11].

One-off simulation sessions are insufficient to bring about a sustained change in clinical practice, and repeated sessions are required to embed and 'normalise' the skills involved [11, 12], with some studies noting that the improvements in team performance seen following a simulation-based intervention are lost if the programme is discontinued [13].

We may see the introduction of compulsory simulation-based assessments, with a required set of 'non-technical skill' competencies to be completed by all Intensive Care practitioners. It is difficult to formally quantify a skill such as leadership or teamwork; however, efforts are being made to standardise the desired qualities of a good Intensive Care team member, with the development of toolkits such as the Ottowa Crisis Resource Management Global Rating Scale [14] and the anaesthetists' non-technical skills checklist [15]. This said, however, it must be remembered that assessments based on simulated performance, though currently used as a supplementary method for judging competence, are of questionable validity.

1.4.3 Virtual Reality Simulation

Virtual reality is emerging as an important educational tool, particularly in surgical procedures such as laparoscopic cholecystectomy, abdominal trauma, neurosurgery

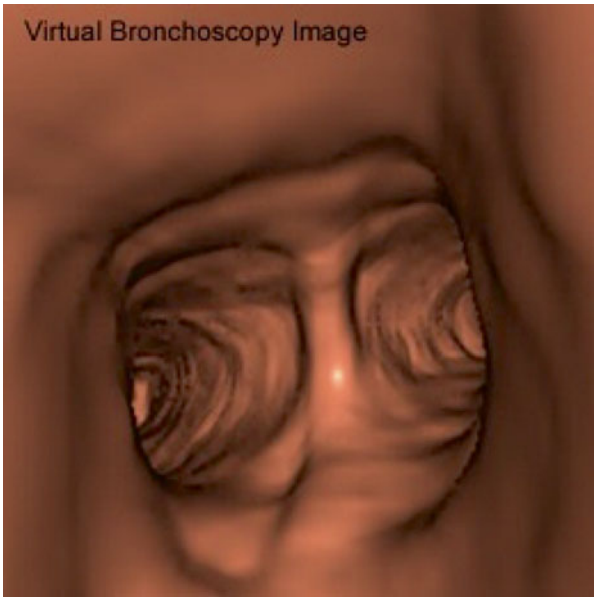

Fig. 1.3 Virtual reality bronchoscopy

and arthroscopic orthopaedic procedures. Virtual reality provides haptic and visual feedback, both effective tools for learning. In the ICU, the concept of virtual reality has been applied to bronchoscopy, where virtual bronchoscopy simulation accurately represents major endobronchial anatomical findings. A prospective study confirmed that an unsupervised training session of virtual bronchoscopy enabled trainees to attain improved technical skills (Fig. 1.3) in terms of dexterity and accuracy, similar to more experienced colleagues. The skills attained were also applicable to the conventional inanimate airway-training model suggesting transferable skills to patient care [16].

1.5 Multidisciplinary and Mobile In Situ Training

Traditionally, simulation training has involved homogeneous groups, for example, medical students, physiotherapists, specialist nurses and anaesthetists. There is now a growing realisation of the importance of multidisciplinary training. In terms of participant feedback, it is most often cited as the best aspect of a simulated scenario. However, this is often difficult to organise, as it requires removing vital staff from the workplace, a particular problem in ICUs. The concept of mobile '*in situ'* simulation has been developed which takes the training to participants in their workplace [17]. Conducting simulation training in active clinical environments appears to increase the element of realism and also provides a familiar environment. Current simulation equipment is now designed to make it easily portable to clinical areas and may allow in situ training to become repetitive, and potentially a routine part of the working week (Fig. 1.4).

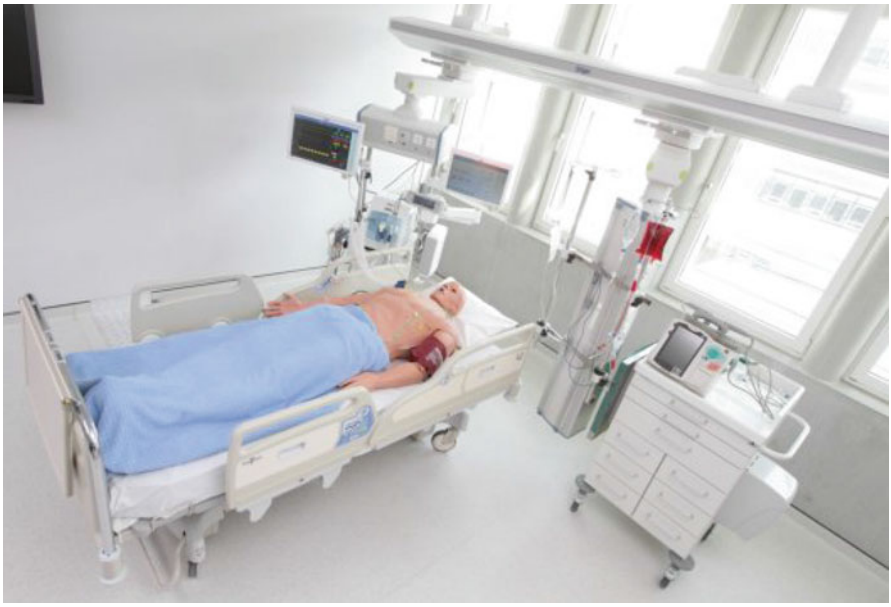

Fig. 1.4 University of Twente, NL. ICU simulation

1.6 Importance of Repetition

It is well recognised that one of the key elements in the success of simulation training is repetition. Regular use of simulation allows trainees to engage in regular self-assessment and correction of errors. Evidence has shown that simulation-based practice yields a dose–response relationship to achieve desired outcomes [18]. To put it simply, the more practice a trainee has, the better the learner outcome is. There is emerging evidence at Kirkpatrick levels 3 and 4 that this form of simulation training does translate into improved patient outcomes [13, 19].

1.7 Integration into Curricula and Regulation

There is evidence of all forms of simulation training occurring in UK ICUs. However, at present, there are no standardised simulation training modules for Intensive Care Medicine trainees in the United Kingdom. The simulation training opportunities are largely institutionally based rather than part of a national programme. With tightening resources it will become increasingly important that simulation training is delivered in a more structured, organised fashion. Other specialties have incorporated simulation into a training curriculum with standardised programmes. Larger standardised training programmes will create the environment for research into the best use of simulation.

There are currently no regulatory bodies overseeing simulation training in the United Kingdom. This is partly due to the multidisciplinary nature of simulation. In the United Kingdom, the Association for Simulated Practice in Healthcare (ASPiH) was formed in 2009 from the merger of National Association of Medical Simulation (NAMS) and Clinical Skills Network (CAH). ASPiH provides a network base for health care professionals that runs simulation training and develop strategic resources for members. The Society in Europe for Simulation Applied to Medicine (SESAM) promotes the educational use of simulation within the European community. In the United States, the Society for Simulation in Healthcare has the same purpose. In the United States, there are several medical research centres using simulation in critical care, for example, The National Institute of Health Clinical Center in Bethesda, Maryland.

1.8 The Future

As technology advances, it is likely that simulation training will become even more realistic, with the development of the perfect 'simulated patient' not far away. There is already a large volume of online learning material, using simulated patients with an array of conditions. In ICU, it will be possible to simulate almost all conditions that we are presented with. Some ICUs already have a permanent simulated patient who is incorporated into the daily ward round for teaching purposes. However, it is likely that the costs of this training may well be a limiting factor. It will also be essential that we do not become dazzled by technology and forget the importance of embedded simulation in a solid educational format. It is crucial that we continue to look for the best and most effective way of utilising this valuable educational resource.

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2 Assessment and Management of the Delirious Patient in the Intensive Care Unit

Valerie J. Page and Annalisa Casarin

Summary of Abbreviations

CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
ICDSC	Intensive Care Delirium Screening Checklist
NICE	National Institute for Health and Care Excellence
PAD	Pain, Agitation and Delirium
RASS	Richmond Agitation Sedation Score

2.1 Introduction

Delirium is very common in critical care [1]. Patients who develop delirium have worse outcomes [2]. It is usually caused by a medical, physiological and/or drug-related event, and until that has resolved the patient will remain delirious. The critical care clinician needs a comprehensive knowledge of delirium symptoms, risk factors and management.

2.2 Delirium Defined

Delirium is a clinical syndrome diagnosed at the bedside. The definition, from the American Psychiatric Association Diagnostic Statistical Manual (DSM) 5, describes core symptoms that can be surprisingly difficult to recognise (Table 2.1) [3].

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_2

Table 2.1 Defining features of delirium according to *American Psychiatric Association Diagnostic Statistical Manual (DSM) 5*

Decreased ability to direct, focus, sustain of shift attention and reduced awareness
Develops over hours or a few days and usually fluctuates in severity within hours
Disturbance in cognition–memory, disorientation, language or perception
Not due to other pre-existing or evolving neurocognitive disorder, not in coma
Evidence of cause, i.e. medical, drug overdose or withdrawal, toxin or multiple aetiologies

Delirium is an acute fluctuating brain dysfunction, which enables it to be distinguished from dementia. Patients with apparent normal cognitive function, through the course of a day, an hour or even a conversation, ramble or become paranoid and deluded. Although hallucinations are common in critically ill patients, they are not required to make a diagnosis of delirium.

2.3 Delirium Motoric Subtypes

Arousal and psychomotor activity changes account for the three clinical descriptive forms of delirium: 'hyperactive', 'hypoactive' and 'mixed' [4]. A patient with hyperactive delirium is easy to recognise, restless, paranoid and never ever seems to sleep. Pure hyperactive delirium, while memorable, is actually uncommon compared with the other two forms, occurring only in 5 % of cases [5]. Most delirious patients in critical care develop hypoactive delirium and generally appear lethargic, compliant and immobile. It is only by interacting with the patient that it can be appreciated they are inattentive and disorientated. With the mixed type of delirium, a patient's behaviour fluctuates, often hypoactive during the day, but increasingly restless, often agitated overnight. Subsyndromal delirium describes a patient who has one or more symptoms of delirium, but does not meet the criteria for delirium diagnosis and does not progress to it [6].

2.4 Size of the Problem

At any one time, an acute hospital with 1000 beds would have around 100 patients with delirium. Delirium affects an estimated 18–35 % of hospitalised elderly, and its incidence in the Intensive Care Unit (ICU) has been documented as up to 82 % [7]. In critically ill patients, it prolongs length of hospital stay by up to 10 extra days, increases the likelihood of discharge to an institution and is a predictor of death [8]. In patients who require mechanical ventilation, those affected by delirium are three times more likely to die by 6 months, and the risk of dying is increased the longer time a patient is delirious [7].

In those patients who survive a critical illness, and developed delirium during the ICU stay, regardless of age, the risk of long-term cognitive impairment following discharge is increased nine times, and it is three times more likely to persist after discharge [9, 10]. This can be equivalent to mild Alzheimer's disease. Patients' quality of life and independence are consequently reduced with high detrimental impact on carers and families, financially and emotionally.

2.5 Risk Factors

Whether or not a patient develops delirium will depend on the risk factors (Table 2.2).

Predisposing factors are those that make a patient more vulnerable to developing delirium following what may be only a relatively mild trigger. They are present on admission and are rarely modifiable: age, history of cognitive impairment, previous episodes of delirium, alcohol abuse, hypertension, age, liver impairment and other chronic medical conditions [11]. The precipitating cause of ICU delirium may be potentially treatable: often an infection or an episode of sepsis, electrolyte imbalance, renal failure, hypercarbia or the use of deliriogenic drugs. Non-modifiable causes would include stroke, traumatic brain injury and pancreatitis. Aggravating risk factors include the use of a bladder catheter, uncontrolled pain, hypnotic and narcotic drugs, visual or hearing impairment and immobility [12]. PRE-DELIRIC is a validated delirium risk prediction score for ICU patients derived from data collected during the first 24 h and is freely available for use [13].

2.6 Routine Monitoring of Delirium

Monitoring delirium is an essential part of routine daily assessment. Ongoing delirium and new delirium is a significant clinical sign. Several studies have demonstrated that clinicians regularly miss delirium in the ICU settings [14]. Most critically ill patients will develop hypoactive delirium, but will be able to obey direct commands, e.g. stick your tongue out, squeeze my hand and usually answer yes to

Table 2.2 Risk factors for delirium in ICU

ICU delirium-modifiable risk factors		Non-modifiable risk factors
Infection	Hyponatraemia	Age, especially over 65
Anticholinergic drugs	Sedative drugs	Cognitive impairment
Opiates	Hypoxia	Dementia
Pain	Hypercarbia	Depression
Immobility	Acidosis	Genetic factors
Dehydration or Constipation	Polypharmacy	Institutionalised residence
Use of physical restraints	Sleep disturbance	
Sensory impairment (visual/auditory)	Use of bladder catheter	

most questions, e.g. do you feel better this morning? In order to detect delirium in critically ill patients, whether intubated or not, clinicians need to use a screening tool or have a meaningful exchange. Routine screening for of all acutely ill hospital patients has been recommended by the National Institute for Health and Care Excellence (NICE) and the Pain, Agitation and Delirium (PAD) guidelines from the American College of Critical Care [15, 16]

Currently, there are two non-verbal screening tools for use in intubated patients, and both are recommended in the PAD guidelines: the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) [17, 18]. They were developed for clinical use and have been validated against the standard *DSM-4* criteria. Both tools can be used in sedated intubated patients for the assessment of delirium; however, patients must be responsive, i.e. able to open their eyes and keep them open in response to a verbal stimulus, usually their name. They require training and practice.

The CAM-ICU is a point in time assessment usually completed twice a shift or when the nurse detects a change in mental status, while the ICDSC is completed during the course of a shift on observing patient behaviour. It is worth specifying that low-arousal states of acute onset with a severely withdrawn patient who does not interact should be recognised as likely indicating delirium.

2.6.1 Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

CAM-ICU (Fig. 2.1) is a modified version of the original CAM screening instrument completed in up to four steps, taking on average 2 min [19]. It assesses four core components of delirium: altered or fluctuating mental status, inattention, disorganised thinking and altered level of consciousness. Before starting, the patient's level of arousal is established using a sedation score such as the Richmond Agitation Sedation Score (RASS) [20].

Step 1. Has there been acute onset of change in mental status? On admission, ask patient's relatives if necessary – 'is your relative/partner/friend behaving normally?' *Has there been a change from the patient's mental status baseline and/or has there been any fluctuation over the past 24 h?*

Step 2. Look for inattention. Is the patient able to pay attention long enough to squeeze the clinician's hand on the 'A's in a 10-letter sequence, such as SAVE A HAART, or A BAD BAD DAY*?*

Patients who are able to squeeze the assessor's hand correctly on the 'A's and not on other letters with no more than two mistakes are negative for delirium, using the CAM-ICU.

Continue only in patients with more than two mistakes on the attention screen:

Step 3. Is the patient drowsy? Or hyperalert?

Patients who fail the attention screen and are drowsy or hyperalert are CAM-ICU-positive.

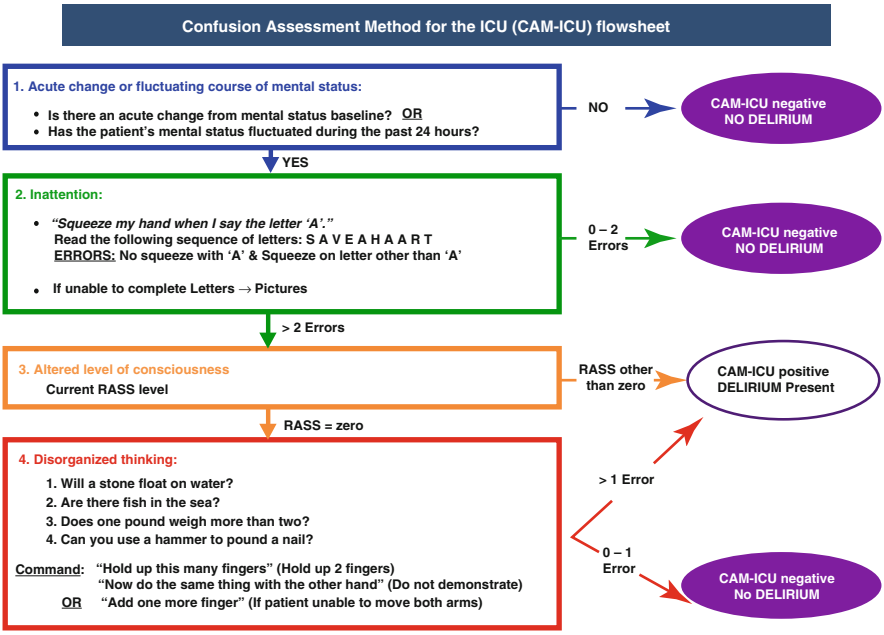

Fig. 2.1 Confusion Assessment Method for ICU (CAM-ICU) flow chart (Copyright © 2002, E. Wesley Ely, MD, MPH and Vanderbilt University. All rights reserved)

Continue in patients who have normal conscious level (step 3 negative).

Step 4. Look for disorganised thinking. Ask the patient four 'yes or no' questions from a choice of two sets provided in the tool and then ask him/her to follow a simple command.

Patients who fail the attention screen and have more than one error in step 4 are CAM-ICU-positive.

In summary, a patient is screened as positive for delirium at that point in time if they have an altered mental status *and* are inattentive *and* show either disorganised thinking or an altered level of consciousness.

2.6.2 Intensive Care Delirium Screening Checklist (ICSDC)

The ICDSC is a checklist of eight items recorded over a period of time, usually a nursing shift [18].

Each item is a common feature of delirium:

- Level of consciousness (only scores in patients not on sedation)
- Inattention (is the patient easily distracted or repeating words/actions? Not thought to be due to sedative drugs)

- Disorientation (time and place)
- Hallucination/delusion/psychosis
- Psychomotor agitation or retardation
- Inappropriate speech or mood
- Sleep/wake disturbance (too sleepy or never sleeps)
- Fluctuation of symptoms

One point is allocated if the nurse detects an item from the list at any time during the course of the observation period. If the patient scores four or more points, he/she is considered to have delirium. If they score one to three, they have subsyndromal delirium. For the ICSDC, the information is readily available, although detecting it relies on subjective interpretation by the observer.

2.6.3 Sedated and Non-intubated Patients

There are a small percentage of intubated patients who will screen positive using the CAM-ICU while on sedation, but following a 2-h sedation hold will screen negative. Early results would suggest that patients with this 'rapidly reversible sedation-induced' delirium appear to have the same clinical outcomes with regard to the length of ventilation and stay in ICU as those who do not screen positive at all [21]. Units using the CAM-ICU may consider additional screening during sedation breaks.

Paradoxically, the CAM-ICU and ICDSC are both highly specific, but lack sensitivity in non-intubated acutely ill patients, i.e. a patient may have delirium, but screen negative [22]. To increase the detection of delirium, use a simple additional test: ask the patient to tell you the months of the years going backwards [23]. If the patient does not engage or cannot complete up to seven months backwards, then that would indicate ongoing delirium [24].

2.7 Managing Delirium in the ICU

New delirium is an important early sign of clinical deterioration; it often precedes other indicators and can enable early intervention.

2.7.1 Treat the Cause

The key to manage delirium lies in establishing and treating the underlying cause(s), whatever is maintaining or has precipitated delirium. In ICU, the common causes are drugs and/or infections. In PRE-DELIRIC, a delirium prediction model for ICU patients, the highest scoring risk factors are coma from any cause, sedatives and infection [14]. Useful checklists include THINK or I WATCH DEATH mnemonics that help with establishing potential causes in individual patients (Table 2.3) [25].

Table 2.3 Two examples of delirium risk factors mnemonics

THINK	I WATCH DEATH
Toxic situations Reversal and aggressive treatment of underlying cause(s) such as CHF and shock Stopping unnecessary deliriogenic agents that may be impairing brain function	Infection: HIV, sepsis, pneumonia
Hypoxemia, or consider giving haloperidol or other antipsychotics	Withdrawal: alcohol, barbiturate, sedative-hypnotic
Infection/sepsis, or Immobilisation	Acute metabolic: acidosis, alkalosis, electrolyte disturbance, hepatic failure, renal failure
Non-pharmacological interventions, such as eyeglasses, hearing aids, reorientation and sleep hygiene	Trauma: closed head injury, heat stroke, post-operative, severe burns
K+ medical management other than new drugs (e.g. correction of electrolyte disorders)	CNS pathology: abscess, haemorrhage, hydrocephalus, subdural haematoma, infection, seizures, stroke, tumours, metastases, vasculitis, encephalitis, meningitis, syphilis
	Hypoxia: anaemia, carbon monoxide poisoning, hypotension, pulmonary or cardiac failure
	Deficiencies: vitamin B12, folate, niacin, thiamine
	Endocrinopathies: hyper/hypoadrenocorticism, hyper/hypoglycaemia, myxoedema, hyperparathyroidism
	Acute vascular: hypertensive encephalopathy, stroke, arrhythmia, shock
	Toxins or drugs: prescription drugs, illicit drugs, pesticides, solvents
	Heavy metals: Lead, manganese, mercury

2.7.2 Non-pharmacological management

Non-pharmacological measures remain the only ones that have been shown to modify delirium and are therefore important to implement [26]. They relate to the unit environment, daily nursing practice and those relevant to the individual patients.

2.7.2.1 'Delirium Bundle'

Unit environmental features to prevent delirium include the availability of windows for natural daylight, avoiding moving patients, noise reduction and clearly visible clocks [27].

Bedside management is recognisable as an excellent nursing care, i.e. frequently orientating the patients, attention to hydration, avoiding constipation, minimising duration of urinary catheterisation, enabling a good night's sleep, use of visual and hearing aids if needed and a familiar nurse [28].

Physiotherapists understand that mobilisation is particularly important for ICU patients from admission. In sedated ventilated patients, it starts with passive limb movement, and with improvement, it progresses up to walking with assistance. Early mobilisation has been demonstrated to decrease delirium and increase the number of patients who achieve normal activities of daily living on discharge [29].

An agitated combative patient whose delusions make him/her challenging and a risk to safety need 1:1 nursing – the nurse will need relieving and assistance regularly – preferably in a calm environment in a side room.

2.7.2.2 Deliriogenic Drugs

Many drugs needed in critical care are deliriogenic, e.g. steroids. Therefore, it is essential to review medication regularly with regards to drug dose and whether they are still required [30]. A significant number of drugs have anticholinergic properties, which when given in combination can aggravate the delirious state, e.g. digoxin, ranitidine, etc [31]. The ICU pharmacist can assist with this intervention.

2.7.2.3 Sedation Protocols

Opioids and sedatives are among the risk factors for delirium, but they are usually required to achieve the goal of a calm and comfortable ICU patient [32]. Pain control is a priority, and finding the correct balance between managing anxiety/agitation and oversedation is a challenge.

Analgo-sedation protocols directed at keeping patients first pain-free and adding low-dose sedative drugs have been shown to decrease the time spent on mechanical ventilation and delirium [33]. Within any agreed protocol, for each ventilated patient, clinicians need to agree the daily sedation target, the sedative drugs and delivery to maintain that and dictate rescue therapy if the patient becomes agitated. Unless there is a clinical reason to keep a patient deeply sedated (e.g. severe asthma) from admission, a daily sedation target should be given to a patient who is awake and calm or easily arousable by voice [34]. Maintaining sedation targets may be achieved with the use of shorter-acting opiate infusions and intermittent boluses of sedative drugs, only as required for interventions. Where infusions of both opiates and sedative drugs are routinely used (which is the case in most of the United Kingdom ICUs) if the patient becomes oversedated, the sedation infusions should be turned off until the desired level of sedation is reached [34]. Sedation breaks are recommended as part of routine daily practice unless the patient is already at sedation target in which case there is no benefit [35]. The aim is to minimise deep sedation without agitation.

Shorter-acting drugs are preferred (i.e. fentanyl or alfentanil) rather than morphine, and midazolam should be avoided because it is long-acting and believed to be deliriogenic [36]. Clonidine, an alpha-agonist with analgesic and sedative properties, can be useful as an adjunct when hypotension is not an issue [37]. Alternative sedative drugs that can be useful and may be used as sole agents are infusions of remifentanil, a very short-acting opioid, or the highly specific short-acting alpha-agonist dexmedetomidine [38, 39].

2.7.3 Pharmacological Management

There is no good evidence to date supporting the use of antipsychotics to prevent or treat delirium in critically ill patients, and they are not recommended other than to help to control the symptoms [17].

2.7.3.1 Hyperactive Delirium

If a delirious patient is agitated, they often require the administration of an antipsychotic. Haloperidol has been shown to decrease agitation, and it is the most common drug of choice in critical care [40]. Even though it can be given intravenously, it can take up to 30 min to take full effect. Due to the uncommon risk of torsades de pointes, which is a dangerous ventricular arrhythmia, haloperidol should not be given to patients with a QTc interval >500 ms, and should be given with extreme care if the QTc is >450 ms [41]. The dose of haloperidol used clinically for delirium has never been established; however, the usual adult starting dose is 2.5 mg intravenously. This can be doubled and repeated once or twice. The British National Formulary quotes a maximum dose of 18 mg in 24 h [42].

While much higher doses have been given in clinical practice, if 10 mg over a short period of time has not worked, it is unlikely that increasing the dose will be successful. It can also cause extrapyramidal symptoms and akathisia, which can be mistaken for restless agitation. Neuroleptic malignant syndrome is a rare complication.

The NICE guidelines support the use of the atypical antipsychotic olanzapine for short-term use in case of psychomotor agitation. Olanzapine can be given intramuscularly (usual dose is 5–10 mg). It can also be given when haloperidol is contraindicated or has not been effective. Regular quetiapine or risperidone are also useful antipsychotic agents. They are given enterally, and the ongoing patient requirement should be reviewed every day [43, 44].

If there is immediate risk to patient or staff safety, midazolam can be used to achieve rapid control. Small doses of benzodiazepines may also be useful where anxiety appears to be a predominant feature. Their use should be limited to the shortest time possible. In general terms, benzodiazepines should be reserved for delirium tremens caused by alcohol withdrawal, because of their deliriogenic properties [45].

2.8 ABCDE: One Approach

Delirium is a complex syndrome with multiple risk factors, many of which are present in the ICU. A strategy that addresses delirium risk factors and management is the evidence-based ABCDE approach developed by the ICU Delirium and Cognitive Impairment Study Group [46]. It combines daily sedation breaks if the patient is not awake, with daily spontaneous breathing trials if the patient fulfils the unit criteria, the review of sedative drugs requirements, delirium identification and management, and early mobilisation.

Fully implementing this bundle has been shown to reduce delirium. Resources are freely available online, www.icudelirium.org

A B	Awakening and Breathing coordination
C	Choice of sedative
D	Delirium identification and management
E	Early mobility

2.9 During and After Delirium

Delirium can be highly distressing for the patient, family and healthcare professionals [47]. Patients and carers need information, both verbal and written, to aid understanding of this distressing experience. While some patients can be left with persistent delirium, the acute episode usually recovers. Leaflets and information to download is available from www.icusteps.org.

2.10 Conclusion

Take delirium seriously; engage the ICU multidisciplinary team; agree local delirium screening and management guidelines; and work towards adherence, so that patients are given the chance of the best possible outcome.

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Management of Stroke in a Non-neurointensive Care Unit

3

Ian Conrick-Martin and Áine Merwick

3.1 Introduction

Stroke is a leading cause of acquired adult disability and is an important growing cause of mortality globally [1, 2].

In an intensive care unit (ICU) setting, stroke recognition and treatment is challenging, from both a diagnostic and management perspective. The situations commonly encountered in stroke management in ICU include development of a new stroke in a patient already being managed in ICU, transfer to ICU of a patient who has recently had a stroke and a patient who does not regain consciousness when anaesthesia/sedation is stopped.

3.2 Stroke Management: Initial Questions

3.2.1 When Did the Stroke Start?

The initial two key questions in a newly suspected stroke is – when did the clinical symptoms start? Is the patient a candidate for thrombolysis/revascularisation?

The affiliation of the author Ian Conrick-Martin is incorrect. For this reason an erratum has been published, correcting the mistake in the previous version and showing the correct affiliation (see DOI 10.1007/978-3-319-22377-3_15).

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_3

Next is the consideration if the patient is a candidate for thrombolysis if the event occurred within the last 4.5 hours, or within 6 hours for anterior circulation cases with large artery occlusion.

The pivotal question is when was the patient last noted not to have the deficit, rather than when was deficit first noted? If the deficit is new and no absolute contraindications are present, thrombolysis should be considered, following emergency imaging and obtaining timely stroke expert advice.

Who to admit to ICU

The intensive care unit (ICU) management of stroke patients focuses on monitoring and optimisation of systemic physiological homeostasis as well as the avoidance of intracranial (and other) complications [3]. Kirkman et al. have made a number of suggestions as to who to admit to ICU, following a stroke [3] (Table 3.1). In the situation of large volume stroke, or following neurosurgical intervention, this may necessitate neuro-ICU admission or ICU admission at a centre with neurosurgical services.

3.3 Stroke Presentations

3.3.1 History and Examination

Stroke is defined as a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than

Table 3.1 Indications for intensive care unit admission following acute ischaemic stroke

Need for intubation and/or mechanical ventilation due to
Decreased conscious level (Glasgow coma scale [GCS] of 8 or less) or evidence of brain stem dysfunction or any other cause of a threatened airway [13]
To prevent aspiration pneumonia in any of the above
Adjuvant therapy for intracranial hypertension or significant cerebral oedema
Acute respiratory failure, for example, due to pulmonary oedema (neurogenic or cardiogenic)
Generalised tonic–clonic seizures or status epilepticus
Apnoeic episodes
Severe stroke (National Institutes of Health Stroke Score >17)
Reperfusion therapy (intravenous or intraarterial), if multiorgan failure present, to manage complications of therapy (haemorrhagic transformation), and in those undergoing local intraarterial therapy
Large middle cerebral artery infarct volume (>145 cm [3]) that predicts a malignant course
Persistent extremes of blood pressure [systolic >220 (in ischaemic stroke patients not undergoing thrombolysis) or >185 (undergoing thrombolysis) or <90 mmHg] that are difficult to manage in a ward setting
Management of organ support, particularly renal replacement therapy and noninvasive ventilation (needed either due to a previous underlying condition, or acute pulmonary oedema, for example) and cardiac dysfunction
Post-operatively, following decompressive craniectomy
Management of the patient with massive/devastating stroke and a high risk of mortality who may potentially become an organ donor

Adapted from Kirkman et al. [3]

24 h or leading to death with no apparent cause other than a vascular origin [4]. Keeping this definition in mind is helpful when reviewing a suspected stroke patient, especially as a history of acute onset focal deficit, is characteristic of stroke. Important from history-taking and examination is to establish if any relevant trauma has occurred that may have contributed to a large vessel dissection or intracerebral haemorrhage (e.g. head or neck injury) or become relevant as a contraindication to specific therapy (e.g. occult fracture). Furthermore, a drug history, especially relating to anticoagulation, antiplatelets or drugs of abuse, is important to obtain and, if necessary, obtain pharmacy records or examine patient's personal belongings. Additionally, information regarding vascular risk factor should be obtained. Identifying if the patient has vomited or is suspected of aspirating is also imperative.

Coma is a rare initial feature in posterior circulation stroke (2 % in one registry study), but it is important to distinguish coma as a result of basilar thrombosis [5]. Useful methods of identifying basilar artery occlusion as a cause of coma include a history suggestive of preceding posterior circulation TIA episodes and sudden onset of coma [6]. Clinical examination findings in posterior circulation stroke may include eye movement abnormalities, focal lateralising signs and pupil abnormalities [6–8]. The predominant features of pontine infarction and/or basilar artery occlusive disease are motor and oculomotor [6–8].

Neurological examination may have to be adapted, and specific factors such as presence of endotracheal tube or sedation in ICU patients should be taken into account. Measuring the level of consciousness and establishing if patient is conscious is imperative, and helpful if measured sequentially in a standardised manner. The National Institute of Health Stroke Score (NIHSS) is a standardised clinical scale used in acute stroke. It is scored from 0 (no deficit) to a maximum score of 42, and includes assessment of the level of consciousness, language, eye movements, visual fields, sensation, sensory extinction inattention, facial and limb weakness, and dysarthria and ataxia [9]. In intubated patients, however, certain components, for example, dysarthria cannot be elicited, and this should be noted.

The majority of stroke patients are managed at the ward or specialist ward (e.g. stroke unit) level. Admission to dedicated stroke units is associated with improved functional outcome [10–12].

However, some patients require admission to ICU for a number of reasons (see Table 3.1), the commonest of those being for mechanical ventilation and/or invasive haemodynamic and neurological monitoring.

Prognostication is important for assessing whether or not to admit to ICU [14]. This should rely on clinical and radiological assessment, with particular emphasis on premorbid function when discussing with relatives. Clear and constructive lines of communication between families, stroke physicians and intensivists are vital.

3.4 Examination

3.4.1 Overall Examination

When assessing a critically ill patient, many tasks happen simultaneously (e.g. treating an immediate life-threatening problem, assessing airway, breathing and

circulation, general clinical examination and focused history-taking from the patient or a proxy such as relatives, medical, paramedical or nursing staff). However, we have described them in a systemic manner here for ease of understanding.

3.4.2 Airway

A number of clinical scenarios can result in airway concerns. Posterior circulation strokes and more particularly those patients with brain stem involvement may have reduced levels of consciousness and be unable to protect their own airway [5–8]. Similarly, those with a degree of cerebral oedema surrounding a large infarct or haemorrhage may have elevated intracranial pressure leading to brain herniation and coma.

It is generally accepted that those with a GCS ≤ 8 are unable to protect their own airway and require endotracheal intubation. Other concerns which may favour securing the airway would include hypoxaemia. However, a larger concern would likely be control of ventilation, and the avoidance of hypercarbia and its deleterious effects on intracranial pressure.

3.4.3 Breathing

Stroke patients may require supplemental oxygen therapy due to aspiration, hypoventilation or both. The percentage of haemoglobin saturated with oxygen remains the greatest variable when describing oxygen delivery to tissues. This has particular relevance when referring to the ischaemic penumbra around an area of ischaemia.

Hypoxaemia is common following stroke and adversely effects outcome. Causes of hypoxaemia following stroke can include aspiration, respiratory tract infection, acute respiratory distress syndrome, pulmonary embolism, pulmonary oedema (neurogenic or cardiogenic) and dysfunction of centrally regulated ventilation.

However, there is some controversy regarding the routine administration of supplemental oxygen which may be detrimental, irrespective of stroke severity [3].

As mentioned above, control of ventilation and specifically CO_2 levels and their consequent effects on cerebral blood flow are of importance, particularly when there is a concern regarding raised intracranial pressure from, for example, an intracranial haematoma, peri-ischaemic oedema or a posterior fossa lesion, where the tentorium cerebelli restricts expansion of oedematous tissue, thereby risking herniation of the brain stem through the foramen magnum.

3.4.4 Circulation

The rationale for treatment of severe hypertension is to lower the risk of haemorrhagic transformation of an ischaemic area (typically large), however aggressive blood pressure reductions may adversely affect cerebral perfusion, especially in the penumbra, thus exacerbating ischaemic damage [3].

Blood pressure should be controlled to ≤185/110 mmHg in patients who may be appropriate for thrombolysis and treatment given to patients who are not thrombolytic candidates whose blood pressure is >220 mmHg systolic or >120 mmHg diastolic on repeated measurements or whose mean arterial pressure exceeds 130 mmHg [12, 15].

Autoregulation is a physiological process which refers to the capacity of cerebral circulation to adjust its resistance to maintain a constant cerebral blood flow regardless of changing systemic blood pressure or cerebral perfusion pressure [16]. An increase in mean arterial pressure (MAP) increases the transmural vessel tension causing an increase in vascular smooth muscle tone (with the converse also the case). It occurs between MAP of 50–150 mmHg, is a very rapid process, and is mediated primarily by endothelium-derived relaxing factor and nitric oxide (EDRF/NO) [17].

Outside these parameters, cerebral blood flow becomes pressure-dependent and directly changes with changes in MAP. In chronic arterial hypertension, the upper and lower limits of autoregulation are both displaced to higher levels, shifting the curve to the right. In hypertensive patients, cerebral hypoperfusion occurs at higher values of MAP, compared with healthy individuals. The limits of autoregulation are affected by various factors, including sympathetic nerve activity, $PaCO_2$ and pharmacological agents. In particular, cerebral autoregulation may be impaired after any brain injury, for example, ischaemic stroke, intracranial haemorrhage or ruptured aneurysm.

A particular note should be paid to the presence of hypertension with bradycardia (Cushing's response), which is associated with severe intracranial hypertension and impending coning.

Systemic examination should include a check for evidence of significant BP arm differences, as stroke may be the presenting feature of acute aortic dissection.

3.4.5 Level of Consciousness and Neurological Examination

A patient's level of consciousness may be assessed by a number of different methods. The 'AVPU' scale describes a motor, verbal or eye-opening response to differing methods of stimuli (Alert/Voice/Pain/Unresponsive). It is essentially a modified assessment of Glasgow Coma Scale (GCS, Table 3.2) [13]. GCS assessment itself may also be used, albeit outside of the context of head trauma for which it was initially designed. However, most clinicians have an understanding of the various components of GCS, and its use in stroke is therefore not unreasonable while acknowledging the limitations of its use in that context.

Eye movement and detecting if eye movement on command can be performed is an important clinical sign to elicit in establishing the level of consciousness, especially in patients who may have brain stem ischaemia.

Table 3.3 lists common and/or useful neurological signs associated with stroke, and Table 3.4 describes the classic stroke syndromes classified by anatomical clinical syndrome and/or vascular territory involved.

Table 3.2 Glasgow Coma Scale [13]

Glasgow Coma Scale (GCS)	
Eyes open	
Never	1
To pain	2
To verbal stimuli	3
Spontaneously	4
Best verbal response	
None	1
Incomprehensible sounds	2
Inappropriate words	3
Disoriented and converses	4
Oriented and converses	5
Best motor response	
None	1
Extension (decerebrate rigidity)	2
Abnormal flexion (decorticate rigidity)	3
Flexion withdrawal	4
Localises pain	5
Obeys commands	6
Total	*(Range 3–15)*

Table 3.3 Stroke signs

Reflex asymmetry
Skew deviation of eyes
Facial asymmetry/facial weakness
Corneal response asymmetry
Tone asymmetry (low tone in hyperacute phase)
Crossed sensory signs
Crossed motor signs
Oculomotor paresis including supranuclear gaze palsy
Upgoing plantar response(s)
Pupil abnormalities
Homonymous quadrantanopia or hemianopia
Flattened nasolabial fold

3.4.6 Environment

General examination of a patient and environmental assessment is an integral part of assessment (e.g. of wallet pockets of clothes) for regular medication etc.

Inspection for rash, for example, as in zoster vasculopathy (as may be seen with chicken pox or shingles), orvasculitis is also important, as it may highlight a potentially treatable cause of stroke [18].

Table 3.4 Stroke syndromes [5–7]

Anatomical clinical syndrome/vascular territory	Clinical features		Mechanism (most frequently)
MCA	Contralateral hemiparesis, hemisensory loss Dysphasia in dominant hemisphere syndromes Inattention/neglect in non-dominant hemisphere syndromes		Cardioembolic or large vessel disease (carotid)
Medulla Medial Lateral (intracranial vertebral artery)	Ipsilateral weakness and later hemiatrophy of tongue Contralateral hemiparesis – arm and leg, hemisensory loss – touch and proprioception Contralateral pain and temperature loss Nystagmus, Vertigo, ipsilateral Horner's, facial sensory loss dysarthria, hoarseness dysphagia Contralateral pain and temperature loss	Contralateral hemiparesis – arm and leg, Hemisensory loss – touch and proprioception Contralateral pain and Temperature loss	Large vessel disease Dissection
Pons	Facial paresis	Hemiparesis	Small vessel disease
	Bilateral hemiparesis – arm and leg, facial weakness, lateral gaze weakness, dysarthria		
Top of basilar	Somnolence, confusion (from thalamic infarction) Bilateral loss of vision, unawareness or denial of blindness (from bilateral occipital infarction)		Embolic
Posterior inferior cerebellar artery PICA	Truncal ataxia, vertigo Truncal lateropulsion		Large artery disease/ cardioembolic
Posterior cerebral artery PCA	Bilateral loss of voluntary eye movements, poor visual–motor coordination, inability to understand visual objects Contralateral hemisensory loss – all modalities, and may have hemi-body pain		Cardioembolic

Additionally, it is important to look for evidences of bruising, which may indicate undisclosed trauma or perianal trauma in the case of 'body packing' of substances such as cocaine. Examination for stigmata of endocarditis or murmurs is worth performing at initial assessment.

3.5 Investigations

3.5.1 Initial Investigations

In the hyperacute phase, blood glucose should be checked as a priority, as hypoglycaemia and hyperglycaemia may mimic stroke syndromes.

In the acute phase, brain imaging urgently with either CT brain or MRI brain is required in suspected stroke to distinguish haemorrhage from ischaemic stroke. CT imaging is fast and usually accessible. In the acute phase, CT imaging with CTA vessel imaging may allow identification of large vessel occlusion or dissection. In many centres, CT and CTA are more readily available in the acute phase, than MRI, and are helpful if MRI is contraindicated. MRI compatibility of devices and monitoring equipment is an additional challenge in ICU patients. MRI brain with diffusion-weighted imaging (DWI) is far more sensitive than CT brain, especially for brain stem ischaemia, although false-negative can occur with early DWI imaging [19, 20]. MRI/MRA with dedicated fat saturation sequences is especially helpful for identifying dissection. MRI can help verify vascular territory (Figs. 3.1 and 3.2).

12-lead ECG should be performed to look for evidence of ischaemia or arrhythmia [12].

Blood gas analysis in the hyperacute setting may provide important measure of haemostasis.

Subsequent and second-line investigations

- Blood and/or urine for drugs of abuse/toxicology (store sample so that it can be checked at a later stage if necessary).
- ESR, cholesterol and lipids, renal profile, full blood count [12].
- Cardiac rhythm monitoring – prolonged rhythm monitoring may be helpful as the yield for identifying atrial fibrillation increases with prolonged monitoring [21].
- Blood culture should be taken if endocarditis is suspected, and a high index of suspicion should be maintained [22].
- Search for underlying mechanism should be commenced, for example, prothrombotic (e.g. occult malignancy, drug-related), specific arterial thrombosis (lupus anticoagulant [LA] and anticardiolipin [ACL]), homocysteine, or small-vessel arteriopathy/ HIV, syphilis, etc. [22].
- CSF testing may be occasionally required in the setting of suspected subarachnoid haemorrhage with negative imaging, or ischaemic stroke with suspected vasculitis or parainfectious aetiology [22].
- Routine inherited thrombophilia screen testing is not justified [23].

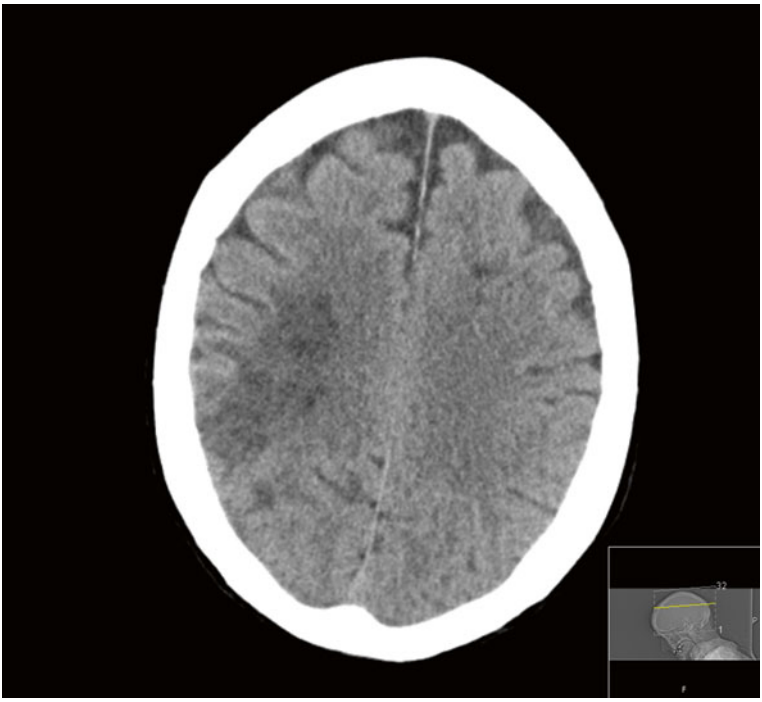

Fig. 3.1 CT brain, axial view. Right middle cerebral artery (MCA) ischaemic stroke

3.5.2 Specific Therapies

Thrombolysis with alteplase is indicated in ischaemic stroke when eligibility criteria are met. Trial data from originally the NINDS trial and the more recent ECASS3 trial provide the basis for licensing of alteplase in acute ischaemic stroke [15, 24]. The open label IST3 trial further supports it use [25]. Registry data from the SITS registry supports its use beyond the setting of clinical trial populations, including in patients over 80 years of age who match the other eligibility criteria [26]. Some controversy exists regarding the strength of the trial data and the effectiveness of the treatment, but appropriate patient selection is pivotal in considering the effectiveness of therapy [27]. Practical difficulties in decision-making regarding thrombolysis include poorly controlled glucose levels, difficult to control BP, significant pre-existing cerebrovascular disease, unclear onset time or concern that a minor deficit may have preceded a more recent deterioration, as well as availability of trained staff and adherence to protocols and guidelines. Although every minute counts in terms of neurons lost, the decision to thrombolyse a patient needs to be made judiciously. Adverse effects of thrombolysis include bleeding risk and allergic reaction. It is important to check blood results when available, e.g. platelets and INR, because although the initial bolus of thrombolytic agent may be given before results of investigations are available, the relevant parameters should be checked before the infusion is given.

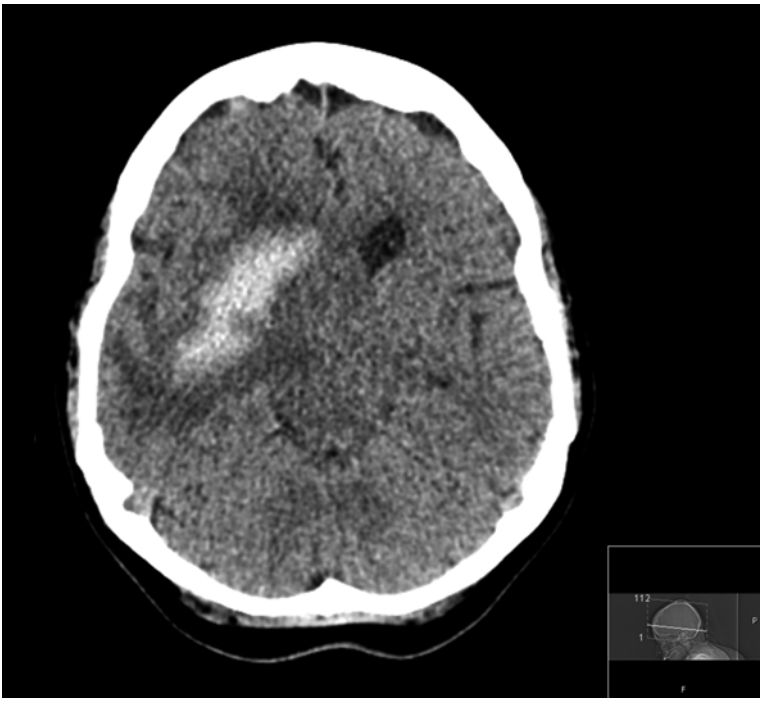

Fig. 3.2 CT brain, axial view. Right cerebral hemisphere intracerebral haemorrhage

Contraindications to tPA based on its license for use include any intracerebral haemorrhage, known or suspected CNS lesion with high likelihood of haemorrhage after tPA (e.g. brain tumour, abscess, vascular malformation, aneurysm, contusion, endocarditis), clinical presentation suggestive of subarachnoid haemorrhage even with normal CT, uncontrolled hypertension (SBP > 180 or DBP > 110 at time of tPA to begin), history of intracranial haemorrhage, active internal bleeding, fracture or acute trauma, stroke, serious head trauma, intracranial or intraspinal surgery within 3 months or bleeding disorder [15, 24].

Recent studies have looked at mechanical treatments include the use of catheters to directly deliver (during angiography) a clot-disrupting or retrieval device to a thromboembolus that is occluding a cerebral artery. Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hours after symptom onset. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy which should be performed as soon as possible after its indication.

Six studies have reported positive results with modern mechanical approaches to re-perfusion. The number needed to treat to achieve one additional patient with independent functional outcome was in the range of 3·2-7·1 and, in most patients,

was in addition to the substantial efficacy of intravenous alteplase [28]. Thrombolysis therapy, despite the low numbers needed to treat to have benefit, will ever only be suited to a fraction of patients who have an ischaemic stroke, especially if there are delays in patients accessing appropriate care [29].

Statin therapy: In ischaemic stroke, statin therapy is suggested for secondary prevention. Although randomised controlled trial (RCT) evidence is strongest for vascular event prevention in large artery disease, there is evidence for efficacy in other stroke subtypes and better prognosis post-stroke [30, 31]. The TIA literature shows a potential protective event with pretreatment with statins, and observational population-based data has shown a positive association between acute statin therapy, survival and improved functional outcome after stroke [32, 33]. Some concerns have been raised regarding statin use and haemorrhage risk, specifically in amyloid angiopathy. However, active statin therapy was not associated with significant increase in ICH in a meta-analysis of 31 randomised controlled trials of statin therapy. A significant reduction in all-stroke and all-cause mortality was observed with statin therapy in intracerebral haemorrhage [34].A retrospective multicentre cohort study of 3481 patients with intracerebral haemorrhage over a 10-year period found that in patients who received statin had better 30-day survival rates following the bleeding event and were more likely to be discharged home or to a rehabilitation centre, despite the fact that statin users had significantly more severe illness and more comorbidities than non-statin users [34].

Antiplatelet usage should be commenced in ischaemic stroke patients as soon as it is practically possible, by whichever route of administration is available, for example, nasogastric tube, per rectum or orally. Antiplatelet agents (e.g. aspirin, dipyridamole or clopidogrel) have similar side-effect profiles, with bleeding, either intracranially or systemically, being the most significant risk. If the patient has been thrombolysed, any antiplatelet usage should be deferred until 24 h after thrombolysis administration, and brain imaging has confirmed that there is no evidence of haemorrhage [24]. Anticoagulation with warfarin or novel oral anticoagulants is used in non-valvular atrial fibrillation [29].

Dual antiplatelet agents (e.g. aspirin and clopidogrel) should probably be reserved for patients with recently symptomatic large-vessel disease high-risk patients, including coronary disease, or patients with stenting [35].

Thromboprophylaxis in ischaemic and haemorrhagic stroke patients should be with inflatable pneumatic compression. The CLOTS randomised control trial RCT showed no benefit of standard thromboembolic deterrent stockings in reducing DVT risk. The CLOTS trial showed that IPC was feasible, safe, and was associated with a 30 % relative reduction in DVT ($p<0.001$) and, more importantly, a 14 % improvement in overall survival to 6 months ($p=0.042$). Although low–molecular weight heparin usage reduces the risk of DVT, it is associated with a greater risk of serious bleeding and no improvement in survival or functional outcomes. IPC in stroke patients have shown improvement in overall survival, but not functional outcomes, and do not lead to a significant gain in quality-adjusted survival [37].

Current data do not support the routine use of anticoagulation for acute ischaemic stroke [12]. Several randomised, controlled trials that used intravenous IV

heparinoids, subcutaneous low–molecular weight heparin (LMWH) or subcutaneous unfractionated heparin (UFH) early after ischaemic stroke failed to show a significant overall benefit of treatment over controls. A systematic review by the Cochrane Collaboration demonstrated that anticoagulation in the first 14 days after stroke (with IV heparinoids, subcutaneous low–molecular weight heparin (LMWH), subcutaneous unfractionated heparin (UFH), oral anticoagulants or thrombin inhibitors did not decrease the odds of death or development of dependency from stroke [38].

Indications currently proposed by some experts for early full-dose IV heparin after stroke or transient ischaemic attack (TIA) include the following:

- Conditions with potential high risk of early cardiogenic reembolisation
- Symptomatic dissection of extracranial vessels (if no large volume acute stroke)
- Symptomatic extracranial or intracranial arteriosclerotic stenosis with crescendo TIAs or early progressive stroke
- Basilar artery occlusion before or after intraarterial pharmacological or mechanical thrombolysis
- Known hypercoagulable states
- Cerebral venous sinus thrombosis

3.6 Systemic Physiological Management

Peri-stroke arrhythmia or dysautonomia may occur, especially with insular stroke. Cardiac rhythm monitoring in the hyperacute time periods has shown QT prolongation in approximately a third of patients, and new onset cardiac arrhythmias (of which atrial fibrillation was the most frequent) were present in 25 % of all stroke patients [39].

Generally, anticoagulation for atrial fibrillation is delayed until 10–14 days post-stroke to minimise the risk of haemorrhagic transformation. If there is another indication for anticoagulation, for example, pulmonary embolism or prosthetic heart valve, the risk of bleeding at the stroke site has to be carefully balanced with the morbidity and mortality risks associated with the indication for anticoagulation, and an informed decision made with specialist input as appropriate. Dose splitting of low–molecular weight heparin may be considered if appropriate.

3.6.1 Glycaemic Control

Management of hyperglycaemia should be similar to that of other acutely ill patients. The NICE-SUGAR study demonstrated in a large, international, randomised trial, that intensive glucose control increased mortality among adults in ICU [40]. Therefore, modest glucose levels of between 4 and 11 mmoL/L are generally accepted as safer targets.

3.6.2 Stress Ulcer Prophylaxis

Critically ill patients are at risk of gastrointestinal bleeding caused by stress ulceration. Agents to suppress acid production are commonly prescribed for patients at risk of such bleeding; histamine-2 receptor antagonists and proton pump inhibitors (PPI) being the commonest such agents. Although the overall quality of evidence is low, it appears that PPIs are more effective in preventing clinically important and overt gastrointestinal bleeding [48, 49]. There is no consistent difference between the rates of ventilator-associated pneumonia, ICU length of stay or mortality in the two groups.

3.7 Cerebral Haemorrhage

Differentiating between a primary haemorrhage and haemorrhagic transformation of an ischaemic stroke can be challenging, but is important, especially from a secondary prevention perspective. Clinical history can be helpful, for example, deficit-maximal at onset, history of previous ischaemic cerebrovascular events, especially as substantial observer variability exists in the differentiation between primary intracerebral haemorrhage and haemorrhagic transformation of infarction on CT brain [41].

Imaging features, for example, evidence of previous lobar haemorrhage from previous or current imaging or hemispheric microbleeds on MRI brain, may point towards amyloid angiopathy and an associated increased haemorrhage risk [42].

An event that respects vascular territory and/ or co-occurs with other ischaemic lesions, including systemic emboli, would increase the probability of an ischaemic aetiology. Haemorrhagic transformation risk is greatest in the first week after stroke, but can occur up to 3 weeks after stroke and occaisonally later.

Reversible cerebral vasoconstriction syndrome (RCVS) may present with both ischaemic or haemorrhagic stroke, including subarachnoid haemorrhage and/or thunderclap headache alone [43]. Reversible cerebral vasoconstriction syndrome may be associated with drugs, for example, sympathomimetics. Bacterial endocarditis is also associated with possible combined haemorrhagic and ischaemic lesions (particularly in multiple vascular territories) [22].

Recommencing anticoagulation of antiplatelets is an area with a paucity of evidence. In patients with atrial fibrillation, the HAS-BLED clinical prediction tool may be used to help guide decision-making [44]. If there are features to suggest amyloid angiopathy, for example, multiple lobar haemorrhages, microhaemorrhages or superficial siderosis without an alternative cause, anticoagulation should ideally be avoided where possible.

3.8 Subarachnoid Haemorrhage

Definitive treatment such as endovascular coiling or surgical clipping may necessitate neurointensive care input, as may treatment for hydrocephalus including placement of an extraventricular drain or insertion of an intracranial pressure monitoring.

The potentially avoidable or treatable complications with subarachnoid haemorrhage include re-bleeding and vasospasm; therefore specialist monitoring and surgical input is required. Managing SAH patients may be challenging, especially if neurosurgical access or bed capacity is an issue; thus, these patients may, by necessity, be cared for on a general ICU while awaiting transfer to a specialist centre.

3.9 Neurosurgical Treatment

Typically, cerebral oedema peaks 2–5 days after infarct onset, and in selected cases, surgical hemicraniectomy or posterior fossa decompression/ shunting may be required, especially in younger patients [45, 46]. People with middle cerebral artery infarction who meet all of the criteria below should be considered for decompressive hemicraniectomy [47]. They should be referred within 24 h of onset of symptoms and ideally treated within a maximum of 48 h [47]. The criteria are as follows:

1. Aged 60 years or under.
2. Clinical deficits, suggestive of infarction in the territory of the middle cerebral artery, with a score on the National Institutes of Health Stroke Scale (NIHSS) of above 15.
3. Decrease in the level of consciousness.
4. Signs on CT of an infarct of at least 50 % of the middle cerebral artery territory, with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or infarct volume greater than 145 cm^3 as shown on diffusion-weighted MRI.

In posterior fossa stroke, neurosurgical intervention may be indicated in the setting of falling level of consciousness attributable to a surgically remediable cause such as raised intracranial pressure or acute hydrocephalus and/or fourth ventricle effacement, for example, due to large-volume cerebellar infarction [12].

3.10 Stress Ulcer Prophylaxis

Critically ill patients, including both ischaemic and haemorrhagic stroke patients, are at risk of gastrointestinal bleeding caused by stress ulceration. Agents to suppress acid production are commonly prescribed for patients at risk of such bleeding, histamine-2 receptor antagonists and proton pump inhibitors (PPI) being the commonest such agents. Although the overall quality of evidence is low, it appears that PPIs are more effective in preventing clinically important and overt gastrointestinal bleeding [48, 49]. There is no consistent difference between the rates of ventilator-associated pneumonia, ICU length of stay or mortality in the two groups.

3.11 Carotid Endarterectomy Perioperative Management

Perioperative management of patients at risk of stroke, for example, carotid endarterectomy (CEA) or high-risk vascular/cardiac procedure may require careful monitoring in a high-dependency or ICU setting to ensure haemodynamic parameters, in particular, blood pressure, are achieved. Administration of antihypertensive medication is recommended as needed to control blood pressure before and after CEA [50]. Clinical findings on neurological examination should be documented within 24 h before and after CEA [50]. CEA may be carried out under general or regional anaesthesia, but in a recent Cochrane review, no difference was found between the outcomes from these two groups [51, 52]. There are a number of important points to note in the perioperative period. These include stable haemodynamics, which can often be challenging at induction and emergence from general anaesthesia, with typical systolic blood pressure goals being in the order of 110–150 mmHg. Clearly, these goals need to be patient-specific and titrated according to the degree of control of hypertension preoperatively; a more rational approach would appear to keep haemodynamics within 20 % of a patient's baseline [54]. The avoidance of both significant hypotension with consequences on cerebral perfusion and of severe hypertension with increased bleeding and risk of stroke would seem wise. It is noteworthy that there are little definitive or robust data to support this (or indeed *any*) strategy.

Regular post-operative neurological observation and examination is mandatory, given the high risk nature of this surgery. Similarly, the presence of ipsilateral neck swelling in the post-operative period should be considered a 'red flag' for an evolving haematoma, which may require urgent surgical re-exploration and may be a significant risk factor for difficult intubation.

Cerebral cooling following stroke is a topic of ongoing studies [55].

3.12 Stroke Mimics and Chameleons

A variety of disorders can mimic stroke, including other disorders that can lead to a 'slow to wake up' ICU patient. Treatable mimics are important not to miss, as are some serious infections such as encephalitis (which may have specific treatments, as well as having infection control and/or public health implications) [6]. Obtaining relevant history regarding exposures, family history and travel is important as is differentiating focal versus global deficits, especially as the differential diagnosis is large (Table 3.5)

Stroke syndromes that masquerades as a different disease state (or stroke chameleons) include bilateral thalamic strokes (resembling global amnaesia), bilateral occipital stroke (resembling confusion/delirium) and infarcts limited to the medial vermis in medial PICA territory usually causing a vertiginous syndrome that resembles a peripheral vestibulopathy.

Table 3.5 Disorders that may mimic stroke

Toxic: Drug-related, especially if drugs have an associated long half-life, or there is associated renal impairment, dialysis or overdose (e.g. tricyclic antidepressants, drugs of abuse) and/or alcohol intoxication (either alone or in combination) or prescription medications in supratherapeutic levels, for example, lithium
Carbon monoxide (may have characteristic radiological features as well as blood gas findings) MRI low or high signal intensity lesions on T1 and high intensity on T2 in the globus pallidus
Hypoxic ischaemic injury
Hypoglycaemia/osmolar/biochemical, for example, hyponatraemia and central pontine myelinolysis
Acute peripheral vestibular dysfunction
Metabolic disorders – including mitochondrial disorders, hyperammonaemia (primary or secondary)
Nutritional, for example, Wernicke's encephalopathy
Neuromuscular – nerve, muscle, for example, critical care neuromyopathy or neuromuscular junction, for example, myasthenia gravis
Infection, encephalitis, or atypical, for example, leptospirosis, west Nile, Whipple's, prion, HIV/HIV-associated
Parainfectious or post-infectious disorder, for example, antibody-associated disorders such as Bickerstaff encephalitis/ Miller Fisher syndrome, ADEM or cerebellitis.
Inflammatory, for example, neuromyelitis optic or multiple sclerosis, especially if brain stem relapse, Behcets, neurosarcoid
Tumour, for example, lymphoma, lymphangitis carcinomatosis or haemorrhage into a tumour, for example, melanoma, thyroid cancer, choriocarcinoma
Venous infarction and secondary haemorrhage due to venous sinus thrombosis
Genetic, for example, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy CADASIL, periodic paralysis
Hemiplegic migraine, including basilar migraine – which may have aura features including vertigo, diplopia, vomiting, but needs to be a diagnosis of exclusion, especially if first presentation or change from typical aura character or duration

3.13 Prognostication and Neurorehabilitation

In ischaemic stroke, blood pressure and stroke severity are the predictors of requirement for ICU stroke management [55]. There is a risk of nihilism with haemorrhage or large ischaemic stroke, and poor outcome may become a self-fulfilling prophecy if early supportive care is not provided. Age, pre-existing functional status and stroke severity graded using the NHISS stroke scale are the most useful factors in prognostication in ischaemic stroke [12, 14]. However, though these factors are useful for group prognostication, they are limited at the individual patient level. Infarct volume is not reliable for prognostication.

High risk of stroke re-occurrence or deterioration in ischaemic stroke patients occurs in patients with acute basilar artery occlusion, having high mortality rates of up to 85 %, especially if there is no arterial vessel recanalisation [6, 7]. Survivors usually are left with significant neurologic deficit. For symptomatic patients who survive, the risk of recurrent stroke is 10–15 %.

Carotid and synchronous middle cerebral artery occlusion is associated with a poor prognosis. Stroke risk is highest in large artery disease (e.g. carotid stenosis) in the days immediately after stroke [57]. It is challenging however to be able to identify which patients are at highest risk of early recurrent stroke, both from a triage and management perspective. Stroke Prognostication using Age and NIH Stroke Scale (SPAN) index is created by combining age in years plus NIH Stroke Scale (NIHSS). The SPAN-100 score which combines the patient age was developed for use in the acute setting of thrombolysis triage, but a reliable externally validated tool for stroke prognosis specifically in an ICU setting is lacking [14].

In intracerebral haemorrhage, anticoagulation use is associated with poor prognosis, as is delay in reversal of anticoagulation [58, 59]. Minimising delay in reversal of anticoagulation represents the most important variable in the oral anticoagulation-related ICH patient prognosis, and reversal should start as soon as possible after symptom onset to prevent haematoma expansion.

Neurorehabilitation is a complex medical and multidisciplinary process. In ICU, important features include patient positioning, skin regimen to minimise risk of pressure ulceration, and attention to bowel and bladder dysfunction [60]. Goal-orientated treatment is an important part of neurorehabilitation. Communication strategies are particularly important and pateints may benefit from speech and language therapy input to help with communication aides such as picture boards. In patients who have a pontine stroke and associated 'locked in syndrome' or deafness, communication strategies are particularly important [61].

3.13.1 Practical Issues in ICU Stroke Management

The requirement for the use of diagnostic radiology in stroke patients often necessitates multiple excursions to the radiology department, which can often be at quite a distance from the ICU. This poses its own issues in terms of assessing the risk/benefit balance posed with intrahospital transfer, with particular concern surrounding the potential for adverse events, reported in a recent study to be up to 22.3 % of intrahospital transfers [62]. These transfers often occur on an 'out-of-hours' basis and with relatively junior staff who can be ill-equipped to deal with such events.

Whilst undergoing a particular radiological investigation, agitation (causing movement artefact) and potential aspiration in the supine position are the two concerns which may require close monitoring.

3.13.1.1 Tracheostomy

Prolonged mechanical ventilation, difficulty weaning from mechanical ventilation and concerns regarding a patient's ability to protect their own airway due to neurological injury may be the factors which would favour the use of tracheostomy. This may have implications for neurorehabilitation, as many such units do not have the expertise to manage such medium–long term airway devices.

3.13.1.2 Feeding

Critical illness is associated with a catabolic stress response. As a consequence, feeding (ideally via the enteral route) should be commenced when it is clinically safe and appropriate to do so [63]. Consideration should be given to long-term feeding with a gastrostomy tube, if prolonged issues with inadequate swallow and high aspiration risk persist.

3.14 End-of-Life Care and Organ Donation

End-of-life issues require sensitivity and planning. Specialist input from a palliative care team can be helpful, particularly with issues around symptom control (e.g. secretion load, breathlessness, distress), which helpfully changes the focus of care to that of comfort and dignity.

In patients who suffer a catastrophic brain injury and in whom brain death has been determined, either by clinical or radiological criteria, consideration should be given to the possibility of organ donation [63]. In the absence of a diagnosis of brain death, the opportunity for donation after cardiac death should be explored, depending on local policies. Patients with a catastrophic spontaneous intracranial haemorrhage often have little or no disease in organ systems and may be candidates for multiple organ donation.

Conclusions and Take-Home Messages

- Stroke is common and potentially associated with significant disability and mortality across age groups
- Disability can be reduced by modern treatments including early supportive care of haemorrhage patients.
- Differentiating stroke from mimicking disorders can be challenging, but is important to recognise as the treatment may vary greatly.
- Identifying stroke mechanism and targeting stroke prevention accordingly are useful especially in ischaemic stroke.
- Safe transfer and early supportive care is important.
- Recent studies show that improved outcome with good blood pressure control in haemorrhagic stroke is an important aspect of stroke management in ICU setting
- End-of-life care should involve a palliative care multidisciplinary team. Organ donation should be considered where appropriate.

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Neuropsychological Rehabilitation for Critically Ill Patients

4

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Summary of Abbreviations

BPS	Behavioural Pain Scale (BPS)
CAM-ICU	Confusion Assessment Method for Intensive Care Unit
CPOT	Critical Care Pain Observation Tool
CRP	C Reactive Protein
ICDSC	Intensive Care Delirium-Screening Checklist
PAD	Pain, Agitation and Delirium
PTSD	Post-traumatic Stress Disorder
RCT	Randomised controlled trial
TBI	Traumatic Brain Injury

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_4

4.1 Introduction

Advances in critical care management have greatly improved survival rates following critical care admission, allowing long-term recovery to take increasing precedence in both the clinical setting and the literature. It is recognised that patient outcome can be negatively influenced by several, if not all, elements of the 'post-intensive care syndrome', a collection of health disorders that are common among patients who survive an intensive care admission. These conditions, such as depression, post-traumatic stress disorder and cognitive impairment have a significant impact on patients' long-term quality of life [1].

The neuropsychological sequelae relating to a critical care admission include intrusive memories, delusions, delirium, panic episodes, nightmares, mood lability, word-finding difficulties, depression, anxiety, post-traumatic stress disorder (PTSD) and cognitive dysfunction. These symptoms affect a high proportion of patients; intrusive and delusional memories have been recognised in 23 and 39 % of intensive care patients, respectively [2]; delirium may be found in up to 65 % of patients [3], and in a recent randomised controlled trial, the incidence of depression after discharge from critical care was found to be 33 %, with up to 7 % of patients satisfying the diagnostic criteria for post-traumatic stress disorder [4]. Rates of PTSD in previous studies have been as high as 27 % [5]. Cognitive dysfunction following a critical care admission has been demonstrated in up to 66 % [6]. In this cohort of 821 patients from a general ITU 3 months after discharge, 40 % of patients had a cognitive level of dysfunction similar to sustaining a moderate traumatic brain injury, and a further 26 % of patients had a level of cognitive dysfunction broadly similar to mild Alzheimer's disease. This was seen to persist in both younger and older adults, and was associated with duration of delirium [6].

When considering the risk of developing psychological sequelae, a prospective cohort study of 157 patients on a general ICU found significant associations between length of sedation and PTSD, benzodiazepine use and depression, and the use of inotropes or vasopressors with anxiety; although when adjusted for acute psychological reactions on the ICU, the strongest independent risk factors for PTSD were mood on ICU, intrusive memories in ICU and psychological history. ICU mood, psychological history and socioeconomic position were the strongest risk factors for depression [5]. Incidence of PTSD has also been shown to be associated with anxiety on ICU, to be independent of physical condition and be reduced by patient reported perceived social support [7]. There are various risk factors that appear to be associated with cognitive dysfunction following critical illness include hypoxaemia [8], dysglycaemia [9], sepsis [10] and delirium [6, 11, 12]. Delirium has many similar and additional risk factors, including age, medical comorbidities, pre-existing cognitive, functional, visual and hearing impairment, barriers to communication, anticholinergic drugs, alcohol or drug withdrawal, infections, iatrogenic complications, metabolic derangements and pain [13].

Rehabilitation after critical illness guidelines were issued by the National Institute for Health and Clinical Excellence in 2009, following the recognition of 'optimising recovery' rather than improving survival as a therapeutic goal. NICE

guidelines highlight both physical and non-physical morbidity following discharge from intensive care, and recommend an assessment of risks and needs of each individual patient, the setting of rehabilitation goals, and ongoing communication with the patient, their family and other health care providers to ensure continuity of care for all patients over the course of recovery. Due to a lack of sufficient published research, it is acknowledged that many of these guidelines are consensus-based rather than evidence-based, and calls for an increase in research focusing on these elements of patient care have been made [14].

4.2 Preventing the Development of Neuropsychological Problems on the Intensive Care Unit

Pain, agitation and delirium are common in critically unwell patients, but are often underdiagnosed [15–18]. These problems are associated with sleep deprivation, hallucinations, distressing dreams and unpleasant memories, and may result in post-traumatic stress disorder and other neuropsychological sequelae [2]. What is also becoming increasingly recognised is that agitation and delirium are also associated with long-term cognitive dysfunction [6]. The American College of Critical Care Medicine/Society of Critical Care Medicine recently developed evidence-based guidelines to aid clinicians in the assessment and management of pain, agitation and delirium, in an attempt to limit the physical and non-physical consequences of these 'symptoms' [19].

The pain, agitation and delirium (PAD) guidelines emphasise that the management of pain should be one of the first steps in the assessment and treatment of the 'agitated' patient. It was concluded that the Behavioural Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) are the most valid and reliable behavioural pain scales for use in intensive care patients who cannot communicate. It is recommended that nurses complete these scores routinely at least four times per day in an attempt to reduce the incidence of unrecognised pain and discomfort. The recommendations for management of pain include routine administration of parenteral opioid medications titrated to pain intensity for non-neuropathic pain, with the addition of enteral gabapentin or carbamazepine for neuropathic pain. The use of adjuvant paracetamol, NSAIDs (although arguably in a limited number of critically ill patients) and ketamine is also recommended. The current research into regional analgesia was felt to be too limited to make extensive recommendations, but stipulations are made for the administration of local analgesia prior to painful procedures. Relaxation methods may also be of use; these could include progressive muscle relaxation, deep breathing exercises and guided imagery techniques [19].

In addition to the management of pain, the guidelines describe the importance of sedation management strategies in an attempt to reduce anxiety and delirium. It is recommended that sedation scores are routinely monitored four times per day, as it has been shown that the use of sedation scores helps to reduce oversedation and reduce the total amount of sedatives administered to patients. The most reliable methods for assessing the depth of sedation to date are the Richmond

Agitation-Sedation Scale [20] and the Sedation-Agitation Scale [21]. In terms of managing sedation, the guidelines advocate minimal use of sedatives, using either a sedative interruption strategy (i.e. spontaneous awakening trial) or a targeted sedation strategy (continuous light levels of sedation). Light sedation is defined as patients being aware and able to follow commands. It has been recommended that non-benzodiazepine drugs (e.g. propofol or dexmedetomidine) are used for sedation where possible, as a recent meta-analysis has confirmed that they are associated with reduced length of mechanical ventilation and intensive care length of stay [22]. It is acknowledged however that benzodiazepines still have an important role in alcohol withdrawal and in other difficult-to-manage situations if other sedative strategies have been unsuccessful [19].

The overarching aim of these guidelines is to prevent delirium, a condition that increases mortality and morbidity following discharge from intensive care [20]. Delirium can present as hypoactive, hyperactive or present with both manifestations, and may contribute to the delusions, nightmares and intrusive memories that follow discharge. However, it is often underrecognised clinically [20], particularly in its hypoactive form, and therefore insufficiently managed. The PAD guidelines recommend that delirium is routinely screened for at least once a day. Assessment tools that should be used for screening delirium include the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC), as both methods have been demonstrated as reliable in bedside Intensive Care Unit (ICU) nursing assessments [23]. The majority of recommended management strategies are non-pharmacological, such as early and progressive mobilisation, sleep hygiene and environment control measures. No specific recommendations for first-line pharmaceutical options have been made, as evidence is lacking or contradictory as to the relative safety and efficacy of different antipsychotics such as haloperidol [24, 25]. Guidelines however do recommend avoiding benzodiazepines following two large multicentre trials that have demonstrated a lower prevalence of delirium in patients sedated with dexmedetomidine compared with benzodiazepines [26, 27].

Landmark studies in the prevention of delirium include the Awakening and Breathing Controlled Trial [11], and work from Schweickert et al. which demonstrated the benefit of early mobilisation leading to better independent functional status and a shorter duration of mechanical ventilation and delirium [28]. These studies led to the development of the ‘ABCDE’ bundle to reduce delirium (awakening and breathing, choice of sedation with fewer adverse effects, daily delirium monitoring and early mobility exercise) [29], a strategy, which can be combined effectively in conjunction with the PAD guidelines described above.

Further pharmacological avenues of prevention include the emerging interest in the potential for statins/or continued statin use to reduce the incidence of delirium through modulation of inflammation. The use of statins on ICU has recently been shown to reduce the incidence of delirium [30, 31], in association with reduced CRP levels [31].

In terms of non-pharmacological interventions music therapy is now a less traditional but often employed early intervention to reduce anxiety and sedation levels

on the intensive care. Music is involved in specific brain functions such as memory and emotion, and has been seen to bring about a state of relaxation, improve temper and increase motivation [32]. From a biological perspective, it can increase the release of endorphins and decrease peripheral catecholamine levels [32]. Potential benefits of music therapy may be a reduction in pain, blood pressure, heart rate, muscle tension and oxygen consumption [32].

A recent randomised control trial has demonstrated reduction in levels of anxiety and sedation requirements in mechanically ventilated patients who self-directed music via headphones whilst on the intensive care unit, compared with patients who had usual care [33]. This study is consistent with the results of a review of randomised controlled trials and semi- randomised controlled trials that have compared music interventions with usual care [34]. However, interestingly, in the recent RCT, there was no difference in the levels of anxiety or sedation between the self-directed music-listening group compared with a self-directed noise block-out group [33], which may indicate a role for control perception in the reduction of anxiety. Authors of the review comment that the quality of the evidence overall is not strong, and that further studies are required and needed, particularly on the effect of a trained music therapist [34]. A clinically interesting study looked at the use of music therapy to assist with respiratory weaning from a ventilator; significant differences were found in heart and respiratory rates between the onset and offset of music therapy sessions, indicating a reduction in anxiety, although no difference was seen in reduction in days to wean between the study and control groups [35].

There is relatively little literature published regarding direct psychological intervention on intensive care, presumably as patients are usually sedated and ventilated. However, at least one study has shown that early psychological intervention for conscious patients, delivered by trained clinical psychologists and nurses, significantly reduced the percentage of patients who required psychiatric medications at 12 months and the likelihood of high risk for PTSD. These psychological interventions consist of stress management approaches, such as cognitive and emotional restructuring, counselling and psychological support, educational interventions and coping strategies. On average, patients receive five to six separate interventions from clinical psychologists over the course of their admission; notably the presence of symptoms of anxiety and depression was reduced, although this effect was not statistically significant [36].

4.3 Neuropsychological Rehabilitation

4.3.1 Transitional Care

It is recognised that the transition from ICU to the ward is one of the most stressful aspects of the ICU experience. Focus groups have demonstrated a sense of abandonment, vulnerability, helplessness, unimportance and ambivalence [37]. In Australia, a role of the ICU liaison nurse has developed to assist in the discharge process, support patients and families, as well as managing medical issues. Subjectively, these

nurses have been found to help patients to feel more safe and confident, calm and settled, relaxed and comfortable, although feelings of uncertainty persist and no difference has been shown in anxiety levels [38]. This role is comparable to that of ICU outreach, although with perhaps a more obvious focus towards psychological and transitional support.

Patients discharged from ICU have complex needs and higher levels of dependence than other hospital patients. In addition to the ICU liaison nurse, several different strategies have been considered and investigated for holistic multidisciplinary ward-based rehabilitation following ICU discharge, some of which are based on established structures for stroke rehabilitation. Several solutions have been considered, including a self-help manual, a roaming specialist team (similar to 'outreach') providing advice rather than services, a roaming rehabilitation team that provides practical treatment, the management of patients on a post-intensive care 'rehabilitation' unit, and the use of a generic rehabilitation assistant who provides practical support to the established ward-based teams [39]. These different approaches all have their own economic and practical issues such as training, division of responsibilities, financing and currently a lack of evidence base. However, they may offer helpful solutions to the problem of post-discharge hospital-based physical and non-physical rehabilitation [39].

Perhaps, a less 'resource-intensive' approach would be a self-motivated rehabilitation strategy. A self-help manual has been shown to independently reduce the incidence of depression and improve self-reported quality of life following discharge from ICU within a post-ICU follow-up programme that begins from discharge to the ward up to 6 months [40]. It may be questioned however that a self-help manual is not appropriate for all patients discharged from intensive care [39].

4.3.2 Patient Diaries

One of the explanations for emotional problems following discharge from intensive care is that many patients have little factual memory of their experiences, and instead have the presence of delusional memories or 'odd perceptual experiences'. Nursing care for patients while in the critical care environment can have a positive effect on psychological well-being. Facilitating communication, explaining care and rationalising interventions, ensuring patients are oriented to time and place (including the awareness of the passage of time due to altered time perception), reassuring patients about transfer and providing patients with information about critical care before admission are all practices that can have a beneficial effect on patient care and symptom reduction [41]. In addition to these informal measures, it may be that patient diaries can help to explain or fill these memory gaps [42].

Internationally and nationally, the use of patient diaries is varied, although they are generally a record of events kept by the nursing staff or family, on behalf of the patient, to be voluntarily read after recovery. Diary use is not yet considered routine practice, with the majority of reported usage being within Scandinavian countries [43] and the United Kingdom [44]. The literature published to date tends to be

positive towards their use; however, there remain questions as to their primary objectives, methodological considerations and efficacy. Some of the methodological concerns are that there is no consistency as to the emphasis of medical-based information versus social or environmental information provided, the number of entries made, or the timing and support at the time of diary provision. Experts comment that although the use of patients' diaries may be very beneficial, improper use or implementation of these diaries could potentially result in poorer psychological outcome, and that further directed randomised controlled trials are required prior to implementation in routine clinical practice [44].

A recent qualitative study on the use of patients' diaries reported mixed emotional feelings following use of the diaries; however, they were viewed by the majority as a positive initiative towards recovery. It was generally seen as a way of gaining a sense of reality, feeling cared for and connecting with loved ones. However, feelings such as shock and fear were also experienced. Despite the negative emotions evoked, all patients felt they would recommend the use of a diary to patients and families on intensive care [45]. Previous research has supported the use of patient diaries to 'help to construct an illness narrative', and reported to have benefits for friends and relatives in supporting themselves and the patient [46]. Using focus groups, these researchers also highlighted that pictures were an important part of the diary, that patients wanted to know how they behaved and what they said whilst on ICU, that the family should be able to write entries and that the optimal timing for the diary handover varies as some patients are ready to read the diary sooner than others [47]. Patient diaries have also been shown to reduce PTSD symptoms [48] and improve Quality of Life [49].

4.3.3 Follow-Up

The handover of a patient diary following ICU discharge can be used as a form of ICU follow-up. However, a more formal follow-up process is now recommended in UK guidelines [14].

A recent review demonstrated a wide variability in the follow-up practice in the United Kingdom [50]. Of those intensive care units that offered a service, one of the similar features was that the clinics were predominantly nurse-led; however, the organisational structure varied between operating principally as a referral service or involving a multidisciplinary team. The referral criteria was found to range from an intensive care stay of 48 h to 5 days, with the time to follow-up spanning the period prior to hospital discharge to 12 weeks after discharge, and the number of follow-up clinics ranging from 1 to at least 3. Attendance rates varied between 30 and 67 % for mixed HDU/ICU clinics; cancellation and non-attendance rates varied from 10–16 to 5–31 %, respectively [50]. Referral to other services was not well reported in the majority of studies included in the review [50]. However, in a previous survey of UK practice, 51 % of ICU follow-up clinics reported not having direct access to other services [51]. The most common symptoms self-reported in the clinics included loss of taste sensation, appetite loss, pruritus, sexual dysfunction,

shortness of breath, mobility problems, tingling sensations in the hands and forearms, amnesia and short-term memory problems, mood changes, anxiety and depression, flashbacks, nightmares and even social isolation [50].

Patients were generally satisfied with follow-up clinics; however, there has been no systematic or objective evidence published in the literature that the clinics improve outcomes in terms of either Quality of Life outcomes or morbidity and mortality [50]. Authors conclude that further work is required to maximise benefits from such services [50]. In Scandinavia, similar conclusions have been drawn following a comparative study of intensive care unit follow-up structure [52].

A recent qualitative analysis following interviews of 34 former ICU patients from all around the United Kingdom demonstrated that patients generally valued some form of ICU follow-up, reporting that the follow-up had an important impact on physical, emotional and psychological recovery in terms of continuity of care, receiving information, gaining expert reassurance and giving feedback to ICU staff. Information about physical, emotional and psychological recovery was particularly important to patients, as was the information that helped them make sense of their ICU experience. Those without access to ICU follow-up care often felt abandoned or disappointed, because they had no opportunity to be monitored, referred or get more information. Some patients found that their health care needs were unmet, because hospitals were unable to provide the specific aftercare they required [53].

A recent multicentre randomised control trial in the United Kingdom investigated the cost-effectiveness of a nurse-led follow-up clinic combined with a self-motivated self-help physical rehabilitation programme [54]. They found that a programme that included a 3-month, 6-month and 12-month follow-up sessions had no significant effect on improved Quality of Life as measured by SF36 self-assessment questionnaires, and therefore that it was not cost-effective to offer this type of follow-up and rehabilitation [54]. Interestingly however, it was demonstrated that intensive care consultant input was required in half of all follow-up visits, specialist referrals and psychology referrals were made in one-third of the patients, and that three-quarters of patients took up the offer to visit the ICU following discharge, indicating that patients were experiencing ongoing problems [54]. The positive effect of visiting ICU after discharge has previously been demonstrated in a qualitative study that interviewed patients who revisited the intensive care unit; patients expressed value in the experience, allowing them to express gratitude, helpful in learning what had happened during their illness and also to suggest improvements [55].

A centre in the United Kingdom found an additional benefit from a patient-focused ‘drop-in’ forum, for patients and relatives to share their experiences in addition to a formal ICU follow-up process [56].

4.4 Cognitive Rehabilitation

Specific cognitive rehabilitative therapies as part of long-term follow-up and rehabilitation are becoming increasingly relevant to the management of patients following discharge from critical care. This is due to the growing evidence that

patients are affected by significant long-term cognitive problems as described above. Cognitive rehabilitation has been defined as 'the systematic, functionally orientated service of therapeutic activities that is based on assessment and understanding of the patient's brain-behaviour deficits'. Cognitive rehabilitation does not focus just on improving memory, but is a functional process that improves insight and awareness and enables an individual to adapt to their environment via targeted external and internal methods such as chunking, and compensatory strategies [57, 58]. Increasingly sophisticated understanding of cognitive processes has revealed fractionated memory and executive function processes that can be captured with more sensitive and more ecologically valid cognitive assessments. Differentiating between impairments in encoding information, storing information and retrieving information can inform targeted cognitive rehabilitation on an individual basis, which has led to the concept of cognitive profiling. This is a move towards holistic rehabilitation that recognises the influences of mood, fatigue and other physiological and psychological factors. This is related to increasing understanding of inhibitory processes that control and regulate cognition, emotion and behaviour, which can be disrupted in disease states and can impact on all aspects of cognitive and emotional processing including perception, attention, memory and executive function and mood regulation. Cognitive rehabilitation is still a growing field, but encouragingly, in relation to cognitive dysfunction following traumatic brain injury (TBI) or stroke, there is sufficient robust evidence to make practice standard recommendations for therapy, such as direct attention training, goal management training and metacognition training, to promote development of compensatory strategies and improve memory and executive functioning, and evidence that comprehensive neuropsychological rehabilitation can improve community integration, functional independence and productivity [57]. It may be that additional psychological interventions, such as Cognitive Behaviour Therapy may be warranted and pre-rehabilitation motivational interviewing, that focuses on motivations, expectations and beliefs, may also have an important role to play in encouraging patient involvement and maximising rehabilitative outcomes.

Of relevance to future strategies for cognitive rehabilitation following discharge from a general ICU are specific research questions such as which patients will benefit? When should cognitive rehabilitation begin? What interventions are effective for intensive care patients [1, 58, 59]? A concept, which may be of relevance here, is that of cognitive reserve. Individuals with less cognitive reserve, influenced by ageing, education and intellectual level, are more vulnerable to cognitive dysfunction following neuronal damage. This has been demonstrated previously in Alzheimer's disease [60] and chronic HIV [61]. This can be seen to relate to the concept of 'frailty' in the critically ill patient and the subsequent increased risk for mortality and morbidity [62].

Several randomised controlled trials into the combined use of physical and cognitive rehabilitation strategies have been initiated to evaluate their utility in improving cognitive, physical and functional outcomes following discharge from intensive care. This is based on the hypothesis that exercise has beneficial effects on

cognition, and potentially the responsiveness to cognitive training, and that the strategic combination of functional training can help assimilate new skills into daily life [63]; in addition, we know that cognitive impairment predicts poor outcome from physical rehabilitation [64]. The RETURN study found a significant improvement in cognitive function following a 12-week programme of rehabilitation compared with the 'usual care' package of sporadic rehabilitation [63]. The ACT ICU trial demonstrated the feasibility of providing combined cognitive and physical rehabilitation for mechanically ventilated patients whilst on the ICU. This study was insufficiently powered to demonstrate a significant improvement in function following these treatments; however, it provides a framework for ongoing investigation [65]. Interestingly, in the recent BRAIN-ICU trial, high levels of depression were found in patients discharged from intensive care with a predominance of somatic rather than cognitive-affective symptoms. It is argued that this may suggest that physical rehabilitation could influence emotional as well as cognitive outcomes [4]. This has been demonstrated previously, following implementation of a structured outpatient-based physical rehabilitation programme, with reduced anxiety and depression levels after 6 weeks [66].

4.4.1 For the Future

Mindfulness meditation is a technique that has been used in other specialities to assist with reducing anxiety, stress and depression, improving attentional processes and coping strategies, reducing mental fatigue, with an overall aim to improve cognitive function and overall Quality of Life. Similar techniques could be used during and following the intensive care unit admission, with both patients and families. This hypothesis has been assessed in a recent randomised control trial investigating mental fatigue following TBI and stroke for patients complaining of isolated mental fatigue. Authors found that there was a significant improvement in mental fatigue, anxiety and depression self-assessment scores, and word fluency and information processing speed, following an 8-week programme using a mindfulness-based stress reduction (MBSR) approach [67]. Potential mechanisms are thought to be mediated by structural changes in brain density in the left prefrontal cortex that are associated with changes in emotion regulation that can impact on cognition, emotion and behaviour [68].

In addition, it is also relevant that relatives of patients admitted to the intensive care suffer significant levels of depression and anxiety during the patients' intensive care stay that persist at 3 months, and develop into post-traumatic stress disorder in up to 30–40 % [69, 70]. These problems are contributed to by anticipatory grief, lack of information on ITU, surrogate decision-making and sleep deprivation. Neuropsychological support may be appropriate and could be incorporated into family-based therapy, which may help the transition towards discharge from hospital and beyond.

Unfortunately however, despite ongoing research, a recent systematic review has failed to demonstrate any cost-effective rehabilitation interventions following

Table 4.1 Neuropsychological rehabilitation options for intensive care patients

On intensive care	Transitional care	Following discharge from hospital
Adherence to PAD guidelines [19]	'Liaison/Outreach' nurse [39]	Patient diaries [45]
Use of the 'ABCDE' bundle [30]	'Self-help' manual [41]	Follow-up clinics [51]
Music therapy [35]		Follow-up visit [56]
Early psychological intervention [37]		Focus/Support groups [57]
		Cognitive rehabilitation in combination with physical rehabilitation [61]

intensive care discharge [71]. The most positive effects were seen for ICU-diary interventions for reducing the incidence of PTSD [48]. The authors conclude that more directed interventions and further research are needed before definitive conclusions surrounding the cost-effectiveness of follow-up and neuropsychological rehabilitation in a resource-limited system can be drawn [71].

4.5 Conclusion

The neuropsychological sequelae following discharge from intensive care have long been underrecognised and therefore neglected. Now that we know of their existence, we can no longer ignore their potentially devastating consequences. In this chapter, we have reviewed some of the potential approaches to prevent and manage these problems, although many of which still require further investigation (Table 4.1). We can go a long way by making small changes in our practice, and continually acknowledging and emphasising the importance of these issues on the ICU. We must also not forget the neuropsychological consequences that a critical care admission and persistent debilitating illness have on friends and family. Interventions that reduce psychological sequelae in significant others would serve to reduce the wider burden of disease and may also help them cope more effectively and aid rehabilitation of post-critical care patients.

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Pain in Intensive Care

5

Harriet Wordsworth and Helen Laycock

5.1 Introduction

Pain, 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage' [1], is the most common symptom reported by patients in intensive care unit (ICU). However, pain is frequently underrecognised and ineffectively managed in the critical care setting [2, 3].

Guidelines produced by the American College of Critical Care Medicine (ACCM) in 2013 highlighted that medical, surgical and trauma ICU patients all 'routinely experience pain' [4]. The incidence of moderate to severe pain at rest in ICU is around 50 %, increasing to 80 % during common interventions and procedures [2, 5, 6], despite the majority of ventilated patients receiving opioids [7]. Effective pain management on ICU poses many challenges as a result of the complexity of the patients' pathology, barriers to adequate assessment and the paucity of evidence for best practice.

5.2 Pain Aetiology in the Critically Ill

Despite the ICU population being heterogeneous in terms of admitting diagnosis, underlying pathology and comorbidities, all are at risk of acute pain. Common sources of pain include:

- Surgical/post-operative: Pain experienced can include somatic, visceral and/or neuropathic pain in patients undergoing elective or emergency surgery.

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_5

- Trauma: This can encompass somatic, visceral and/or neuropathic pain at potentially multiple sites and can be complicated by traumatic brain injury, which hampers evaluation and risks the development of headache syndromes.
- Sepsis: The incidence of moderate to severe pain in medical patients is equivalent to that of surgical or trauma patients. However, often the intensity reported by medical patients is more severe [2], and there is emerging evidence that sepsis-associated inflammation could lead to a hypernociceptive state [8].
- Immobility: A lack of mobility in the critically unwell can lead to muscle stiffness, arthralgia, pressure ulcers and painful neuropathies.
- Indwelling devices: These are frequently used in ICU and may not always be considered as a source of pain but include tightly fitting face masks, endotracheal tubes, urinary and vascular catheters.
- Procedural pain: Procedures essential to patient care can produce pain, and this can be particularly intense during endotracheal suctioning, chest-drain removal, wound care and repositioning of patients [9].
- Chronic pain: Patients admitted with pre-existing chronic pain conditions are at risk of exacerbation of their pain as a consequence of their current medication being discontinued through fear of side effects in the critically ill, potential interactions with other therapies or unavailability of usual routes of administration.

5.3 An Introduction to Pain Physiology

Patients in intensive care can experience a number of different types of pain that have different mechanisms and may require different management. The commonest types of pain that occur in the intensive care unit are either nociceptive, arising from the stimulation of nerve endings by mechanical, thermal or chemical stimuli, or neuropathic arising from a lesion of the peripheral or central nervous system.

Pain, as described as a sensory and emotional experience, is therefore not a consequence of peripheral stimulation alone. The experience of pain occurs as a result of the peripheral signal being transmitted to and interpreted by the central nervous system; four main processes can explain this.

5.3.1 Transduction

This is the processing of mechanical, thermal or chemical stimuli into the common ‘signal’ of an action potential in the primary sensory neurone. Chemical messengers arise as a result of tissue damage and immune activation, and include histamine, bradykinin, adenosine triphosphate (ATP), hydrogen ions, potassium and prostaglandins. These compounds then activate ligand-gated or voltage-gated ion channels in the nerve terminal, causing depolarisation and the generation of an action potential. Other mediators in the inflamed tissue, such as substance P, sensitise the nerve fibres to depolarise at a lower threshold potential.

5.3.2 Transmission

Noxious stimuli are then transmitted via the primary sensory neurone to the central nervous system via the dorsal horn of the spinal cord. Here, the majority of primary afferent neurones synapse in the superficial laminae, whilst a smaller proportion synapses in the deeper laminae. They connect with either the interneurons, involved in the modulation of pain at a spinal level, or the second-order neurones which transmit noxious stimuli to the thalamus and cortical pain matrix, via the spinothalamic pathway, and to the brain stem via spinoreticular and spinomesencephalic pathways to initiate autonomic responses.

5.3.3 Perception

The brain allows for the integration and interpretation of pain inputs. Second-order neurones synapse with areas referred to as the 'pain matrix'. This consists of the primary and secondary somatosensory cortex as well as areas involved in the more affective components of the pain experience, such as the anterior cingulate cortex and the insula.

5.3.4 Modulation

Pain perception is intrinsically modulated via facilitatory and inhibitory mechanisms, both spinally, at the level of the dorsal horn interneurons (see above), and by descending control from higher centres such as the periaqueductal grey and medulla.

5.4 Consequences of Pain in the Critically Ill

Pain is a symptom that has far-reaching consequences in the critically ill (Table 5.1).

Table 5.1 Consequences of pain in the critically ill

Physiological	Psychological	Ethical	Financial
Augmented stress response	Anxiety	Suffering	Increased ventilated days
Respiratory complications	Depression	Failure to adhere to legal responsibility?	Increased length of stay
Delayed wound healing	Post-traumatic stress disorder	Breach of Hippocratic oath?	Increased total use of medication
Development of chronic pain		Breakdown of trust with family	
Consequences of reduced mobility, e.g. thromboembolic, musculoskeletal			

5.5 Physiological Effects

The stress response to pain is thought to trigger pathophysiological mechanisms leading to hyperglycaemia, cortisol secretion, catecholamine release and the secretion of anti-diuretic hormones [10, 11]. This is evidenced by studies demonstrating a correlation between pain scores and plasma levels of stress hormones in the post-operative period [12] and studies of perioperative analgesia, indicating a less exaggerated stress response when regional anaesthesia and effective pain relief are used [13, 14]. It is thought that activation of the autonomic system, as seen in the surgical stress response, is in part due to pain [15]. Therefore, pain may cause an amplified stress response in patients who already have a severe inflammatory burden, resulting in greater physiological disturbance.

Pain can have an impact on ventilation. Inadequate analgesia in spontaneously ventilating patients predisposes them to atelectasis, and subsequently hospital-acquired pneumonia and hypoxaemia. Although the majority of evidence comes from surgical rather than medical patients, there is a correlation between high pain intensity and poor respiratory outcomes [16, 17]. It also impacts on mechanically ventilated patients. Merely assessing pain has been shown to correlate with a reduction in the duration of mechanical ventilation [18] and a decrease in nosocomial infections [19]. Respiratory and musculoskeletal physiotherapy is important for improving mobility, weaning from mechanical ventilation and global functional recovery. Pain has been shown to be a barrier for initiating and adherence to such programmes [20].

Wound healing may also be improved, indirectly, by providing effective pain relief. Subcutaneous partial pressure of oxygen is increased post-operatively in those with adequate analgesia [21] and therefore could reduce the incidence of wound infection [22].

5.6 Development of Chronic Pain

Chronic pain is a well-recognised complication of acute pain. Both medical and surgical patients who recall experiencing pain whilst on ICU show a higher incidence of chronic pain [23]. The incidence of post-ICU chronic pain is between 30 and 40 % at 6 months and can significantly impact on both physical and emotional rehabilitation [24]. This incidence is higher than other chronic post-interventional pain states such as post-thoracotomy pain [25] and post-mastectomy pain [26]. ARDS and sepsis are also associated with the development of chronic pain in large cohort studies [24, 27].

Changes in excitability in peripheral nociceptors (peripheral sensitisation) or in the dorsal horn and/or brain (central sensitisation) through exposure to repeated stimuli and mediators of tissue injury are thought to contribute to the development of chronic pain along with a reduction in the descending inhibitory pathways. Furthermore, long-term structural and functional damage to the neurones predispose the patient to developing neuropathic pain [28].

5.7 Psychological Effects

Acute psychological disturbances such as anxiety and depression, as well as feelings of helplessness and nightmares have all been associated with inadequate analgesia [3] in the critically ill. Long-term follow-up of ICU patients has also revealed the correlation between acute pain and the development of post-traumatic stress disorder (PTSD) [29].

5.8 Ethical Consequences

Failing to provide a patient with the basic right of comfort whilst ill could be seen as a breach of their human rights. Whilst controversial, there could be a legal right to effective analgesia, and certainly physicians should consider whether inadequately addressing pain is against both the Hippocratic oath and Declaration of Geneva.

5.9 Financial Impact

There is also a financial incentive for the health care provider to deliver appropriate analgesia; the I-SAVE study showed nearly a $1000 saving per ICU hospitalisation when patients received a protocolised analgesic and sedation regimen [30]. A reduction in total length of hospital stay, reduction in duration of mechanical ventilation and total usage of analgesic and sedative agents were also observed in a group of trauma patients, after a protocolised analgesic and sedation plan was implemented [31].

5.10 Pain Assessment

Traditionally, it was assumed that the ability to perceive pain relied on a level of consciousness to enable interpretation of the nociceptive input. Painful stimuli in the periphery ascend, via the thalamus, to the somatosensory cortex (primary areas) and other higher order (secondary) areas such as the amygdala and insula, which coordinate a behavioural reaction to this stimulus. However, functional MRI has shown activation of both primary and secondary cortical areas, even when the patient clinically has a severely deranged level of consciousness [32]. Inconsistent voluntary and non-voluntary behavioural responses are also seen in patients in the minimally conscious state, indicating some degree of pain perception [33]. Therefore, an altered level of consciousness cannot be interpreted as an inability to perceive pain, but it does make its assessment challenging.

Consequently, guidelines for the assessment of pain on the ICU take this into account [4], suggesting pain is assessed regularly in all patients, recommending certain validated tools for specific circumstances.

5.11 Self-Report Scales

Pain, a subjective experience, may not correlate to the perceived severity of an insult as it is based on prior experience, pain thresholds, emotional state, comorbidities and physiological response to the injury. Consequently, the 'gold standard' for assessing pain is self-reporting, where the patient commonly evaluates pain intensity using a predetermined scale of numbers or words. In those able to communicate in ICU, an enlarged version of the numerical rating scale (NRS) has been shown to be the most valid and feasible method [34].

5.12 Behavioural and Surrogate Scales

In ICU, a self-report of pain is often limited by an inability to communicate. Patients may have an altered level of consciousness as a result of an underlying pathology, delirium or sedative medication. In these circumstances, pseudo-objective tools are useful, and the ACCM guidelines [4] recommend the use of either the Critical Care Pain Observation Tool (Table 5.2) or the Behavioural Pain Score (BPS) (Table 5.3)

Table 5.2 The Critical Care Pain Observation Tool [36]

Indicator	Description	Score
Facial expression	No muscular tension observed	Relaxed, neutral: 0
	Presence of frowning, brow-lowering, orbital tightening and levator contraction	Tense: 1
	All of the above facial movements plus eyelid tightly closed	Grimacing: 2
Body movements	Does not move at all (does not necessarily mean the absence of pain)	Absence of movements: 0
	Slow cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection: 1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking staff, trying to climb out of bed	Restlessness: 2
Muscle tension	No resistance to passive movements	Relaxed: 0
	Resistance to passive movements	Tense, rigid: 1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid: 2
Compliance with ventilator	Alarms not activated, easy ventilation	Tolerating ventilator or movement: 0
	Alarms stop spontaneously	Coughing but tolerating: 1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator: 2
OR vocalisation (extubated patients)	Talking in a normal tone or no sound	Talking in normal tone or no sound: 0
	Sighing, moaning	Sighing, moaning: 1
	Crying out, sobbing	Crying out, sobbing: 2

Scores for each domain are summed giving a score of 0–8

Table 5.3 The Behavioural pain scale [35]

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g. brow-lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilator	2
	Fighting ventilator	3
	Unable to control ventilator	4

Scores from each domain are summed, giving a score from 3 to 12

[35, 36] after subjecting a number of behavioural tools to psychometric analysis for reliability, validity and feasibility.

These tools are appropriate for any adult ICU patient without traumatic brain injury who is unable to communicate but able to produce a motor response. The BPS produces a score for facial expression, upper limb movement and mechanical ventilator compliance, whilst CPOT also includes scores for muscle tension and vocalisation. These tools may be influenced by medications and observer bias, but remain the most feasible for use with ICU patients at present.

Other possible methods of evaluating pain such as surrogate pain reporting and evaluating changes in physiological variables have both been demonstrated as unreliable in the ICU setting [3, 37].

5.13 Management of Pain on Intensive Care: General Principles

Pain management in intensive care is complex. It should involve utilising both pharmacological and non-pharmacological interventions, evaluating their effect and also ensuring analgesia is used pre-emptively before procedures known to be painful (see above). Additionally, regular reassessment, after a change in analgesic management, and reaction to changing patient needs remain the best ways to improve pain management in critical care, regardless of the choice of therapy.

Unfortunately, this issue is complicated by the overlap between sedation and analgesia. Many analgesics have sedating effects and are often used in combination with sedatives to produce ‘sedation-analgesia’. In the past, pain was incorrectly attributed to inadequate sedation, and managed by deepening sedation rather than addressing the real problem of inadequate analgesia [38]. Many studies have examined the relationship between levels of sedation and clinical outcomes such as length of stay and length of mechanical ventilation, and it appears that the overall benefit of lighter sedation outweighs the risk [39–41]. The ideal regimen would allow for

Table 5.4 Pharmacokinetics and pharmacodynamics of opiates commonly used in intensive care

Drug	Onset (IV)	Equipotency (IV)	Elimination half-life	Context-sensitive half-time	Metabolism
Morphine	5–10 min	10	3–4 h	NA	Hepatic glucuronidation with some active metabolites (M6G)
Fentanyl	1–2 min	0.1	2–4 h	200 min (6 h infusion) 300 min (12 h infusion)	Hepatic glucuronidation
Methadone	1–3 days	Conversion ratio increases as the dose increases	15–60 h	NA	Hepatic demethylation
Remifentanil	1–3 min		3–10 min	3–4 min (3 h infusion)	Non-specific plasma and tissue esterases
Hydromorphone	5–15 min	Conversion ratio increases as the dose increases	2–3 h	NA	Hepatic glucuronidation

Modified from Barr et al. [4]

the manipulation of sedative medication for levels of sedation to be as light as possible, or to at least enable daily sedation interruption whilst providing ongoing analgesia.

5.13.1 Pharmacological Management

5.13.1.1 Opiates in Intensive Care

The majority of sedated ventilated patients will be prescribed a regimen which will include an opiate [7], and intravenous opiates remain the recommended first-line agent for managing non-neuropathic pain on intensive care [4] (Table 5.4).

A European-wide study of ICU physicians enquiring about preferred analgesics showed that the most commonly used analgesic agents were morphine (33 %), fentanyl (33 %) and sufentanil (24 %) [42]. The choice of opioid and dose depends on several factors, including the pharmacokinetic and pharmacodynamic profiles of the medication (see Table 5.4) as well as the patients' needs and morbidities. However, common pharmacological perceptions of plasma half-life and drug potency should be taken in the context of the analgesic effect produced in the individual, as such perceptions may lead to underdosing.

Meperidine is usually avoided in the ICU population due to the risk of neurotoxicity, and agents with agonist-antagonist action should be used judiciously due to the potential for ceiling effects and withdrawal reactions in opioid-tolerant patients.

There is no conclusive evidence to suggest the optimal opioid for use in the general adult ICU population; however, the method used to initiate and titrate the analgesic may have more of an effect on clinical outcome. The ACCM guidelines do not stipulate whether a bolus regimen or continuous infusion, or indeed a combination of the two, is most appropriate, although there is some evidence that combining infusions with intermittent boluses leads to improved analgesia [19, 31].

5.13.1.2 Adjuvant Analgesics in Intensive Care

The side effects of opioids are well known, and the use of non-opioid methods of analgesia should be considered wherever possible as for both multimodal analgesics and opiate sparing.

- *Paracetamol* can be used in most patients, even in those with end-stage liver disease, as long as appropriately reduced daily doses are prescribed [43].
- *Non-steroidal anti-inflammatory agents*. The use of non-steroidal anti-inflammatories is a risk-benefit decision in the individual patient. Whilst the analgesic effect might reduce the amount of opiate required, the critically ill patient is already at higher risk of developing renal failure, peptic ulcer disease and acute cardiac events due to their pro-inflammatory, often hypotensive state, and the use of NSAIDs may compound this risk. Unfortunately, there is very limited evidence about the efficacy of NSAIDs and paracetamol in ICU settings, and practitioners generally extrapolate knowledge from post-operative studies [44].
- *Gabapentin* has been shown to reduce opioid consumption in neuropathic populations on ICU and so should be considered if there is a described or potential neuropathic element to the pain [45].
- *Alpha-2 agonists*. Dexmedetomidine is gathering support as a sedative agent on ICU, especially in patients at risk of delirium, and has some intrinsic alpha-2-mediated analgesic properties [46]. Although no evidence has demonstrated superior analgesia in the ICU setting, alpha-2 adrenoreceptor agonists (including clonidine) and NMDA antagonists (including ketamine) should be considered if pain management is problematic.
- *NMDA antagonists*. Ketamine is also now widely used in patients with pain unresponsive to opiates and for procedural pain such as dressing changes. It has the benefit that it confers few cardiovascular side effects in the critically ill. Analgesic doses are infrequently associated with the psychotropic side effects, especially if co-administered with sedative agents [47].

5.13.1.3 Analgesic Protocols in Intensive Care

Whatever the pharmacological agents chosen, there are clear benefits to using a protocolised analgesic regimen in response to regular pain assessments [30, 31]. Such protocols should incorporate input from the entire multidisciplinary team to ensure a holistic package to improve the patient experience and enable enough flexibility to tailor them to the individual needs.

5.13.1.4 Regional Anaesthesia in Intensive Care

The use of regional anaesthesia in ICU is still debated and as such the ACCM only recommend it for a sub-population where its benefit has been strongly demonstrated; the use of thoracic epidural analgesia in those undergoing abdominal aortic aneurysm repair has been shown to improve post-operative pain relief compared to intravenous opiates and is associated with very low complication rates [48].

Concerns about increased infection rates and coagulopathy have limited the use of continuous peripheral nerve blockade, and ICU admission has been highlighted as an independent risk factor for complications [49]. Again, an individualised risk-benefit assessment should be made for the use of regional anaesthesia in critical care.

5.13.2 Non-pharmacological Therapy

Non-pharmacological interventions should be considered for every patient as an adjunct to pharmacotherapy, because they have limited side effects, are often inexpensive and can provide engagement for the family.

Simple interventions such as ensuring appropriate patient positioning and splinting of traumatic injuries can reduce pain. Music therapy, massage, relaxation exercises and acupuncture have all been studied to a limited extent, but currently no strong evidence exists specifically for intensive care patients [50, 51].

5.14 Procedural Pain

Providing effective analgesia for procedure-related pain in ICU is extremely important. Up to 80 % of patients experience pain during routine procedures, such as turning, or tracheal suctioning.

The Thunder II Project [9] identified observable pain-related behavioural responses to ICU procedures and showed that patient turning was associated with the highest pain intensity (4.93 on a NRS out of 10), followed by drain removal (4.67), wound care (4.42), tracheal suctioning (3.94), central venous catheter placement (2.72) and femoral sheath removal (2.65).

Several studies have shown that pre-emptive analgesia (both pharmacological [52] and non-pharmacological, e.g. relaxation [51]) significantly reduces pain behaviours during chest-drain removal, and should be considered for all types of procedural-related pain [4].

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Regional Anaesthesia in the Intensive Care Unit

6

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6.1 Introduction

Pain is a common problem in Intensive Care patients. Pain is a modifiable risk factor for sleep deprivation, delirium and post-traumatic stress disorder [1–3]. Regional anaesthesia (RA) has the advantage of providing non-sedating targeted analgesia. Dynamic pain is better controlled with RA than opioid analgesia [4], assisting early mobilisation of patients [5]. RA may also decrease the incidence of chronic pain [6].

6.2 General Principles

Regional anaesthesia (RA) uses local anaesthetic (LA) agents to block conduction of nociceptive impulses in nerves arising from targeted areas of pain. Single injections of local anaesthetic agents have a limited duration of action, typically 12–24 h. To extend the duration of nerve blocks, perineural catheters can be sited next to the appropriate nerve or plexus.

Liposome-encapsulated bupivacaine, with duration of action of 72 h, may eventually negate the need for catheters and infusions in epidurals and peripheral nerve

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_6

blocks [7, 8]. More research needs to be done to ascertain safety and efficacy, and it is currently only approved by the FDA for infiltration at surgical sites.

6.3 Risks of RA

6.3.1 Local Anaesthetic Systemic Toxicity (LAST)

High LA plasma levels can cause neurotoxicity (culminating in seizures) or cardiac toxicity (culminating in refractory cardiac arrest), and may arise acutely from inadvertent intravascular administration of LA during block placement, or, more insidiously, from progressive systemic absorption of LA from the site of injection. Toxicity depends on the peak plasma concentration, which in turn depends on the dose, the site of injection, absorption and metabolism.

The rapidity of absorption of LA is highest in intrapleural and intercostal spaces. Toxicity can also result from infusions if the rate of administration exceeds the rate of LA metabolism. Most LA agents depend on hepatic metabolism and renal excretion. The minimal effective dose of LA should be used in patients with excretory organ dysfunction and in blocks where the absorption of LA is high. In patients with hepatic dysfunction, the doses should be decreased [9]. In renal failure, active metabolites may accumulate, although there have not been reports of these causing toxicity in humans. The incidence of toxicity is 0.01–0.2 % [10].

Lipid emulsion improves the chance of successful resuscitation from LA-induced cardiac arrest and must be accessible as an emergency drug in all facilities where local anaesthetics are administered [11].

6.3.2 Nerve Injury

Most RA-related nerve injuries are neuropraxias that ultimately recover. The incidence of permanent nerve injury is approximately 0.03 % [12, 13].

Nerve injury is likely to be multifactorial, and there is no evidence to prove the superiority of any technique for nerve localisation (nerve stimulation or ultrasound) in preventing nerve injury [14].

6.4 Overview: RA Techniques Relevant in ICU

Several peripheral techniques may be encountered in the post-operative/critical care setting. Table 6.1 summarises different types of anaesthetic techniques that could be considered for intensive care patients. Upper and lower limb plexus blocks are commonly used for analgesia. They can also be used to block sympathetic autonomic supply to the limb, improving blood flow to the limb. Blockade of the femoral nerve may provide excellent analgesia in patients with femoral fractures and after knee surgery; the procedure is technically easy and is amenable to catheter placement for prolongation of the block, and can be done in the supine

Table 6.1 Common regional analgesic techniques and corresponding Intensive Care indications.

Regional anaesthesia technique	Indications
Superficial cervical plexus block	Central line insertion
	Analgesia for tracheostomy (bilateral blocks needed)
	Analgesia for superficial procedures on the anterior neck to the clavicle
	Infiltration below sternocleidomastoid investing fascia allows deeper procedures on the neck (blocks the deep plexus)
Limb plexus blocks	Analgesia in the distribution of the plexus
	Sympathectomy to enhance limb perfusion
	Limb ischaemia
	Re-implantation surgery
	Plastic surgery flaps
Interscalene blocks	Analgesia for shoulder, upper arm (interscalene)
Supraclavicular, infraclavicular, axillary blocks	Analgesia for arm, forearm, hand
Femoral nerve block	Femoral fractures (catheter technique allows prolonged effect)
	Knee surgery
	Analgesia for anterior thigh, medial lower leg
Sciatic nerve block	Analgesia for posterior thigh, lower leg, ankle
Paravertebral, intrapleural, intercostal blocks	Unilateral block of intercostal nerves for thoracic, abdominal analgesia
	Alternative to epidural
	Bilateral placement possible, but rapid LA absorption increases LAST risk
TAP block	Analgesia of anterior abdominal wall
Epidural	Extensive bilateral dermatomal cover of thorax, abdomen
	Sympathectomy

position. The interscalene approach to the brachial plexus allows insertion of a catheter for prolonged LA infusion, and has been shown to be useful for control of the severe pain that typically follows injury or surgery to the densely innervated shoulder joint. It can also be used to provide sympathectomy and improve perfusion in arm ischaemia, as a rescue therapy after inadvertent vasoconstrictive intra-arterial injection, and for improving perfusion to reconstructive plastic surgical flaps. Bilateral superficial cervical plexus blockade provides analgesia of the anterior neck, which can be useful to facilitate the performance of a percutaneous tracheostomy.

6.5 Superficial Cervical Plexus Block

Blocking the nerves of the superficial cervical plexus is useful for insertion and suturing of central lines and superficial cutaneous procedures between the jaw and the clavicle. Bilateral blocks provide cutaneous anaesthesia when placing tracheostomies. The trachea is innervated by the vagus and sympathetic trunks. Trans-tracheal injection of LA or nebulised lignocaine can be used to anaesthetise the tracheal wall.

The cervical plexus is formed by the anterior rami of the upper four cervical nerves and is divided into superficial and deep plexuses. The superficial cervical plexus becomes subcutaneous below the midpoint of the sternocleidomastoid muscle. Branches include the lesser occipital nerve, the great auricular nerve, the anterior, middle and lateral supraclavicular nerves, and the transverse cervical nerve (Fig. 6.1). The nerves are easily blocked by infiltrating local anaesthetic from the midpoint of sternocleidomastoid along its posterior border, below the platysma.

The external jugular vein crosses sternocleidomastoid at this point and must be avoided.

The investing fascia of the sternocleidomastoid communicates with the deep cervical fascia, allowing local anaesthetics placed beneath the investing fascia reach the deep plexus [15].

Ultrasound can be used to identify the investing fascia of sternocleidomastoid, and to place the local anaesthetic below it. Spread of the local anaesthetic along these fascial planes allows the block to be used for deeper surgery on the neck, including end arterectomy.

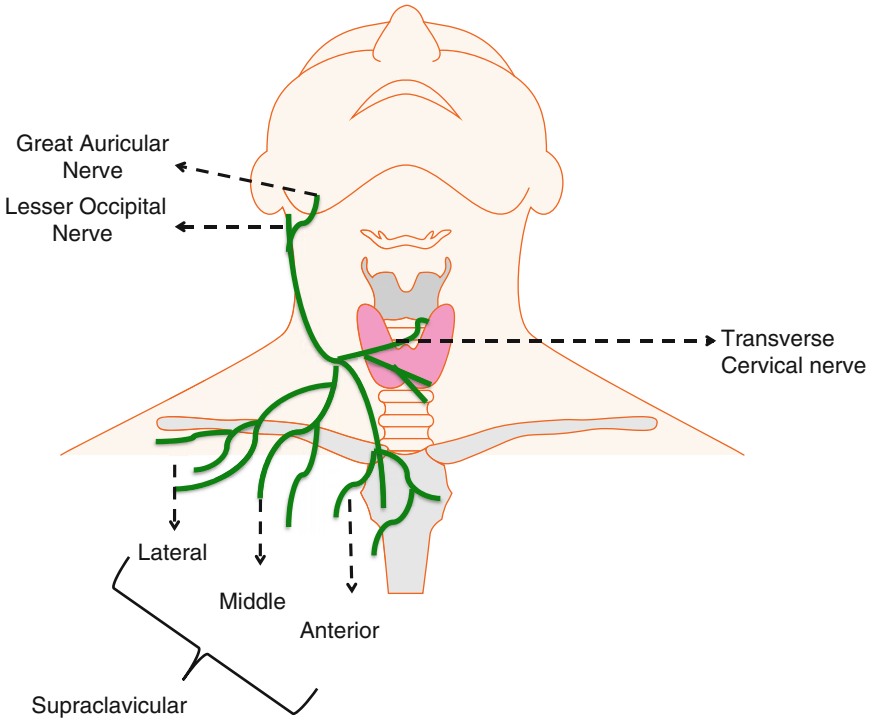

Fig. 6.1 Distribution of the branches of the superficial cervical plexus (illustrated in *green*)

6.6 Epidural Analgesia

Epidural analgesia (EA) involves the prolonged instillation of local anaesthetic (LA) drugs into the epidural space (ES), a potential space within the vertebral canal between the dural membrane (which invests the spinal cord) and the inner surface of the vertebrae. The segmental nerve roots (SNR) all traverse the ES. A volume of LA solution introduced into the ES will spread craniocaudally and block nerve conduction in SNRs within its area of spread. As the SNRs include sensory nerve fibres (including those for dull and sharp pain), motor nerve fibres and (in thoracic and lumbar segments) sympathetic nerve fibres for each body segment, EA conveniently establishes a band of dense analgesia for multiple contiguous body segments from a single instillation point. The initial number of dermatomal segments in this band is determined primarily by the volume of LA solution instilled. The ES is also convenient for placement of an indwelling catheter, through which an ongoing infusion of LA solution can be administered to maintain the established block.

EA is most efficient at controlling pain from intensely painful distinct anatomical lesions (such as a surgical incision, localised burn or localised traumatic injury). For optimal efficiency, the catheter should be sited at the physical vertebral level corresponding to the dermatomal level of the lesion; thus, to efficiently cover the upper abdomen and thorax, a thoracic site of insertion is required [16].

Use of LA in moderate concentration is central to EA function. If it is necessary to extend EA over many dermatomes, larger volumes of LA solution will be needed, necessitating reduction in LA solution concentration to reduce LAST risk. As solutions become more dilute, analgesic density may diminish. It is an accepted practice to add low-dose lipophilic opioids (such as fentanyl) to EA mixtures to compensate, although these actually act systemically. Epidural morphine establishes useful analgesia at spinal cord level, but occasionally causes late respiratory depression and cannot independently ablate movement-associated pain.

6.6.1 Benefits of EA

EA, using LA, provides analgesia quality superior to that achievable with systemic analgesics such as opioids [4]; it is especially effective at reducing pain during movement, including respiratory movement. By preventing nociceptive impulses from reaching the spinal cord, it may prevent the initiation of intraspinal nerve conduction pathway remodelling found in chronic pain syndromes [17, 18].

In published studies, EA has been associated with interim benefits: (1) reduced pain scores when compared to systemic analgesia [4]; (2) reduction in requirements for opioids for post-operative pain, with reduced opioid adverse effects [18]; (3) decreased rate of graft occlusion after lower-limb peripheral vascular disease surgery [19]; (4) thoracic EA (TEA) reduces ventilated days post abdominal aortic aneurysm surgery [20]; TEA reduced pain and respiratory dysfunction in patients with multiple fractured ribs [21] and (5) TEA showed to be beneficial as therapeutic sympathectomy for cardiac surgery [22].

TEA is the central anaesthetic technique adopted in several multidisciplinary "fast-track" clinical pathways for oesophagectomy, colonic surgery and upper abdominal surgery, which have been associated with shorter duration of ICU and hospital stay [23, 24]. TEA is also useful in post-thoracotomy pain reduction programmes [18].

6.6.2 Contraindications, Limitations and Risks

Safe proficiency in EA placement, especially Thoracic Epidural Analgesia (TEA), requires considerable training. Vertebral anomalies occasionally preclude EA placement, even by skilled practitioners. Inadvertent dural puncture leads to cerebrospinal fluid (CSF) leak and debilitating headache, and spinal cord injury may rarely occur with dural puncture during TEA. Transient neuropathy can also occur, albeit with a low risk of permanent injury. Catheters should be securely fixed to skin to prevent movement, but catheter migration can still occur, usually back out of the ES causing EA failure, although instances of late dural penetration have been documented. It is imperative to ensure that the volumes of LA used in EA are not inadvertently infused into the subarachnoid space and CSF.

EA is contraindicated by local sepsis at the planned insertion site, and is discouraged in the presence of systemic sepsis. Catheter infection from bacterial migration from the insertion site and from unsterile injection technique is possible.

Unpredictable variation in ES anatomy (blood vessels, fat, fibrous septae) limits predictable consistency of both catheter sitting and LA spread. An isolated SNR may remain unblocked due to local anatomical factors despite good LA spread to surrounding segments. These patient factors, in combination with the ever-present possibility of catheter migration, mean that a proportion of EA will fail for technical reasons, and a 'backup' analgesic strategy must always be planned. Even when blocks initially work well, repeated clinical assessment of nociceptive sensory dermatome level (using cold stimulus, which correlates with nociception) and overall efficacy of block is required to titrate appropriate continuation dosing. This can be labour-intensive, and requires trained staff.

Epidural blood vessels are at equal risk for injury during catheter insertion and withdrawal. An expanding epidural haematoma will compress nerve roots or spinal cord and may lead to paraplegia. Clinical signs are subtle, and MRI confirmation and surgical decompression within 8 h are essential for there to be a chance of avoidance of permanent neurological fallout. EA is thus contraindicated in patients with significant coagulopathy or thrombocytopaenia. Any catheter manipulation must be temporally separated from the administration of therapeutic anticoagulants; current local consensus guidelines as to anticoagulant timing for patients requiring EA must be followed [25].

Thoracic and lumbar SNRs are accompanied by the sympathetic nerves, which are invariably blocked by even low-concentration LA; hence, a sympathectomy is an unavoidable consequence of EA. The wider the segmental band of analgesia, the more extensive is the sympathectomy, which additionally extends two to three

segmental levels higher than the level of sensory block. It is occasionally therapeutically useful: cardiac sympathectomy by thoracic EA may reduce heart rate and arrhythmias after ischaemic heart disease surgery [22], EA reduces graft failure after peripheral vascular surgery [18], microvascular perfusion and function of the gut may be improved [25]. Frequently, however, sympathectomy-induced venodilation reduces cardiac preload, causing hypotension. Bradycardias may also occur. Significant hypotension may result in patients being given more fluids, more blood products and vasopressors, all with attributable risks that may outweigh the benefits of the EA. The hypotension may be especially difficult to manage in patients with other coexisting causes of hypotension such as systemic inflammatory response.

6.6.3 Overall Risk: Benefit Assessment of EA and Its Impact on Mortality

Assessing the role of EA as a general management strategy in the intensive care unit is complicated. Studies specifically evaluating RA of any form in critically ill patients are rare [26, 27]; thus, extrapolations from studies in the overall surgical population must be made. Few studies of EA in the overall surgical population evaluate mortality as a primary endpoint, and many are underpowered. The weight placed by prominent recent meta-analyses on intra-operative events complicates extrapolation of their results to the post-operative period relevant to intensive care [28].

The large randomised controlled MASTER trial, assessing EA (447 patients) versus systemic analgesia (441 patients) in high-risk patients undergoing major abdominal surgery or oesophagectomy with mortality as a primary endpoint, failed to demonstrate mortality benefit (5.1 % EA, 4.3 % control, $p=0.67$) even on subgroup analysis [29], although EA patients had lower pain scores and lower respiratory failure incidence (23 % EA, 30 % control, $p=0.02$) [30]. The 2013 ACCCM Pain, Agitation and Delirium guidelines were able to recommend thoracic EA for patients after abdominal aortic aneurysm surgery, but found inadequate, or conflicting, data in other areas; hence, no recommendation could be made for thoracic EA in non-vascular abdominal or thoracic procedures, or for lumbar EA [31]. A 2014 meta-analysis, usefully focusing on the post-operative value of EA when compared to systemic analgesia, assessed 9044 patients from 125 studies over 42 years. The authors claimed to demonstrate a small mortality benefit for EA when compared to systemic analgesia only (variably reported as 3.1 % vs 4.9 %, 2 % vs 3.2 %, and 1.8 % vs 2.4 %, depending on the trial inclusion criteria), and showed that EA was associated with reduced Odds Ratios less than 1 for atrial fibrillation, supraventricular tachycardia, respiratory depression, atelectasis, pneumonia, ileus and post-operative nausea, but also confirming substantially increased Odds Ratios for hypotension in EA. This study's four-decade inclusion period has drawn criticism, but it supports relative safety of EA, a trend to respiratory benefit, confirms the risk of hypotension and suggests a small mortality benefit (of the order of 2 % for EA vs 3 %) [32]. Substantiating these apparently small mortality differences by

randomised controlled trials will require an enrolment in excess of 8000 patients [30, 32], which may never be practically feasible.

It may therefore be reasonable to suggest that EA be selectively considered for individual patients. Those most likely to benefit include patients with painful injuries where reduction of systemic analgesia side effects is important (such as the elderly), while TEA may be of benefit in limiting respiratory complications and cardiac arrhythmias in patients with chest or upper abdominal surgery or rib fractures. In all cases, these benefits must be weighed against the risks of EA, especially in patients with clotting disorders and pre-existing causes of hypotension or haemodynamic instability.

When segmental blockade is desirable, but risks of EA appear unacceptable, other RA techniques may be of benefit.

6.6.4 Alternatives to EA

6.6.4.1 Paravertebral Block

LA in the paravertebral space provides a unilateral block of nerve roots. The extent of the block is variable: a single injection of 0.3 mL/kg usually provides a block of three to five segments. For more extensive blocks, multiple injections may be needed. Catheter techniques are commonly used to provide prolonged analgesia [33].

The efficacy of the block is comparable with EA for thoracotomies, and has been used for analgesia for flail chest, open cholecystectomies and nephrectomies [34].

There are specific advantages over EA. The unilateral blockade of the sympathetic trunk results in lower incidence of hypotension and urinary retention. It is technically easier to site than TEA, and may be safer than TEA in patients with coagulation abnormalities, as it does not carry the risk of epidural haematoma formation. The intercostal vessels are, however, in close proximity to the space and can be damaged during the block. It is a deep and non-compressible space, and risk benefit must be considered when placing the block in patients with coagulation disorders.

There are cautions: In 10 %, the LA will spread (via the intervertebral foramina), giving a bilateral block. Incidence of epidural spread is increased with ultrasound techniques [33, 34].

If the block is placed too laterally, it will be an intercostal block and only cover a single dermatome.

There is a 0.5–1 % risk of pneumothorax. There is the rare possibility for the dural cuff to extend more laterally than anticipated and for LA to be injected subdurally, resulting in an extremely profound neuroaxial block. Absorption from the paravertebral space is rapid, and LA doses need to be controlled to prevent LAST.

6.6.4.2 Intrapleural Block

Intrapleural blocks provide unilateral analgesia for chest and abdominal surgery as well as for chronic cancer pain and pain in pancreatitis [35]. LA is injected between the visceral and parietal pleura, blocking ipsilateral intercostal nerves. The LA may also track medially, blocking the sympathetic chain and splanchnic nerves. Infection, pleural adhesions, pleurodesis, effusions and haemothorax will make the block

ineffective. It is also contraindicated in patients with bullous lung disease, where the risk of pneumothorax is increased. Because the phrenic nerve is blocked with intrapleural anaesthesia, caution should be used if the patient has contralateral phrenic nerve paralysis.

In patients with intercostal drains, this technique can be used via the intercostal drain, provided it is safe to clamp the drain to allow the local anaesthetic to bind. If the drain cannot be clamped because of the risk of pneumothorax, then intrapleural blocks are less effective as the LA is lost via the chest drain. The block is gravity-dependent: spread of LA to block upper intercostal nerves and thoracic ganglia and ipsilateral stellate ganglion can be encouraged by using a 20 degree head-down position. Side effects include a pneumothorax rate of 0.3–2 %, LAST, Horner's syndrome and phrenic nerve blockade [35].

6.6.4.3 Transversus Abdominus Plane Block

This is a unilateral field block of the nerves to the anterior abdominal wall in the fascial plane between transversus abdominus and internal oblique muscles. It is useful as an adjunct for procedures involving somatic pain on the anterior abdomen. Visceral pain is not blocked. Injection at the Triangle of Petit blocks T7–L1. For upper abdominal analgesia, subcostal TAP blocks can be performed [36]. Volumes of 0.3–0.5 mL/kg are required. Frequently, bilateral or four-quadrant blocks are needed, requiring attention to the dose of LA used. Catheters can be placed to prolong the block. LA spread is variable and dependent on the block technique: most spread is anterior. Posterior spread to the paravertebral space is possible, although unpredictable [37]. The block can be used in anticoagulated patients. Side effects include bowel injury, and hepatic and splenic injury with subcostal blocks [38].

Conclusion

There is a range of available RA techniques which may be applicable to critical care, all of which have the potential to provide analgesia superior to that of systemic analgesia.

While it may not be possible to demonstrate unequivocal mortality benefit for the use of RA, superior analgesia and interim benefits (such as reduced rates of pulmonary complications) make them worth considering for specific patients in the intensive care.

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Dynamic Assessment of the Heart: Echocardiography in the Intensive Care Unit

7

Carlos M. Corredor

7.1 Introduction

Echocardiography provides useful information for the diagnosis and management of haemodynamically unstable patients in the intensive care unit (ICU). Simultaneous visualisation of structure and function of the heart, coupled with the ability to monitor in real time the results of therapeutic intervention makes echocardiography an instrumental tool for the critical care physician. The last few years have seen giant leaps on the diagnostic quality of new portable devices and digital storage management systems, improving the reliability of bedside echo studies.

A growing body of evidence suggests that echocardiography can positively impact the management of critically ill patients [1–4]. International bodies recognise the growing role of echocardiography in the ICUs and have developed guidelines to ensure adequate standards for training and practice [5, 6].

7.2 Indications for Echocardiography in ICU

Indications for echocardiography in the ICU can be divided in diagnostic, monitoring and guidance of interventions. A single echo examination can serve multiple purposes.

The British Society of Echocardiography (BSE) graded individual clinical conditions in which the use of echocardiography is 'indicated' or 'not indicated' [7]. Many of these conditions are relevant to the critically ill patient. The American College of Cardiology Foundation (ACCF), in partnership with the American Society of Echocardiography, published practice guidelines for the appropriate use criteria for echocardiography in 2007. The 2011 update contains a section that specifically addresses 'Transthoracic Echocardiography (TTE) for Cardiovascular

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_7

Table 7.1 Indication for echocardiography acute care setting

BSE	ACCF/ASE
Indicated	***Appropriate***
Chest pain with haemodynamic instability	Hypotension/haemodynamic instability of uncertain or suspected cardiac aetiology
Assessment of the presence of complications following MI	Acute chest pain with suspected MI, inconclusive ECG during pain
Persistent hypotension of unknown cause	Suspected complication of MI
Suspected pericardial tamponade	Respiratory failure/hypoxaemia of uncertain aetiology
Suspected or established PE to inform decision regarding thrombolysis	Guide therapy of known acute PE
Infective endocarditis (characterise valvular lesions/ complications	Severe chest trauma with suspected cardiac injury
	Uncertain
	Assessment of volume status of critically ill patient
	Inappropriate
	To establish diagnosis of acute PE
	Routine evaluation of mild chest trauma

BSE British Society of Echocardiography, *ACCF* American College of Cardiology Foundation, *ASE* American Society of Echocardiography, *PE* pulmonary embolism, *MI* myocardial infarction

Evaluation in the Acute Setting'. In this document, clinical indications were developed by a panel of experts and scored independently by a separate panel on a scale of 1–9. Use of echocardiography was considered appropriate (score 7–9), uncertain (4–6) and inappropriate (1–3) [8] (Table 7.1).

7.3 Focused Versus Detailed Echo Examination in ICU

Characteristics unique to the critically ill patient and the ICU environment make the bedside TTE examination different to a 'standard' echocardiography exam. Factors such as mechanical ventilation and limitations in positioning the patient in the ideal left lateral decubitus for echocardiography can preclude the acquisition of good quality images in certain windows. The effect of acute pathology, inotropic medication and intrathoracic pressure in normal physiology further compounds the interpretation of spectral Doppler haemodynamic values.

In common with other imaging techniques, a limitation of echocardiography is operator experience and skill. The performance and interpretation of a full echo examination in ICU requires significant training and expertise.

There is however evidence that bedside-focused screening TTE can positively influence management of the critically ill patient and can uncover unsuspected cardiac abnormalities, prompting more detailed investigations [9].

Several protocols are currently in existence for focused echocardiography in the critically ill patient. The Focus-Assessed Transthoracic Echocardiography (FATE) protocol [10], the Focused Echo Evaluation in Life Support (FEEL) [11], the Focused Assessment with Sonography in Trauma (FAST) [12] and The Focused Intensive Care Echo (FICE) are examples of commonly used protocols.

The common denominator to these protocols is a systematic examination in the context of the clinical situation. The FICE protocol has been specifically designed for the assessment of the unstable critically ill patients

7.4 Standard Basic Windows

A focused echocardiography examination of the critically ill patient should include two-dimensional (2D) images of the following views or windows (Fig. 7.1), (Table 7.2):

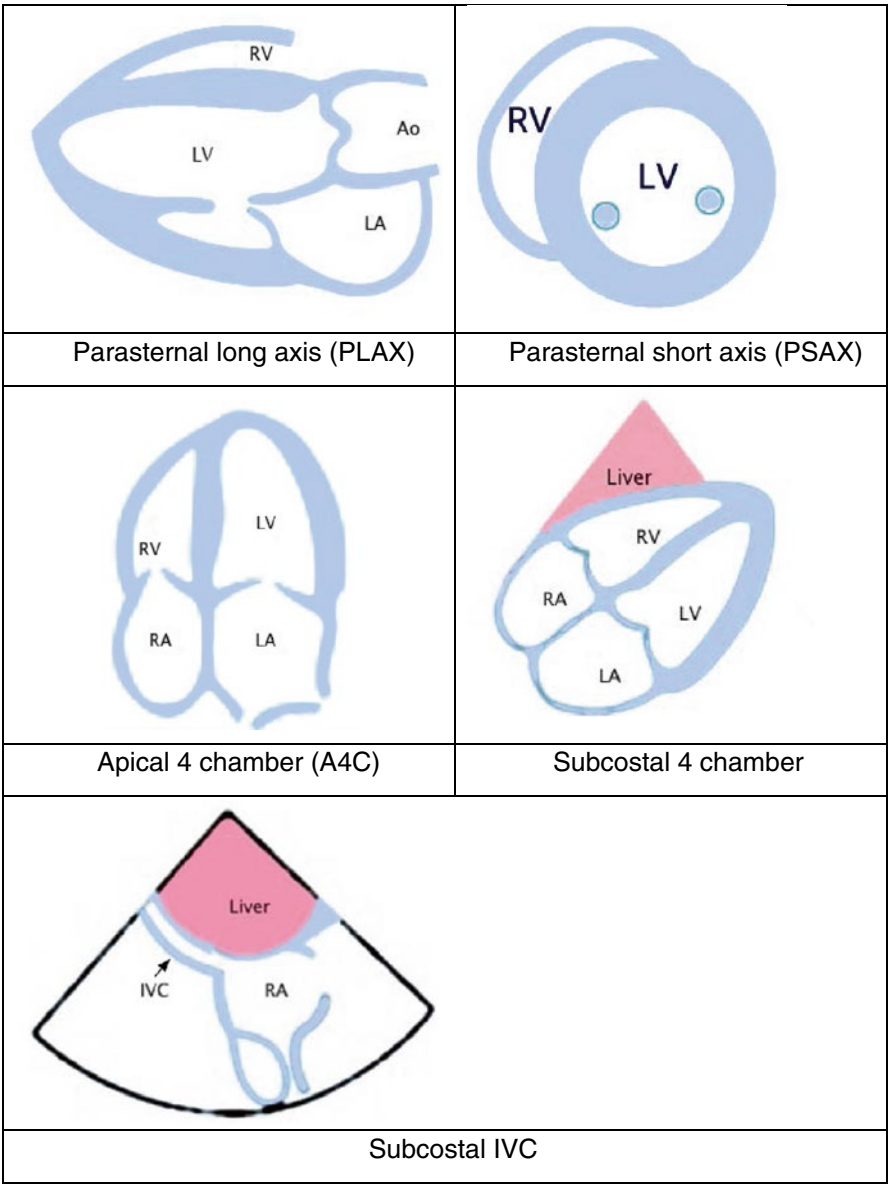


Fig. 7.1 Focused echocardiography transthoracic windows

Table 7.2 Basic transthoracic echocardiographic windows, tips for obtaining each view and utility of each window

Windows	Obtaining this view	Utility
Parasternal long axis (PLAX)	Third to fourth intercostal space, left parasternal border. Transducer index marker points to right shoulder	LV size and function RV size Pericardial and left pleural effusion Aortic dissection Aortic and mitral valve
Parasternal short axis (PSAX)	Third to fourth intercostal space, left parasternal border. Transducer index marker points to left shoulder	LV /RV size and function Pericardial effusions
Apical four chamber (A4C)	Fourth to fifth intercostal space, midclavicular line. Index marker points towards left	LV/RV size and function Mitral and tricuspid valves Atrial size (RA, LA) Pericardial effusion
Subcostal four chamber	Transducer flat in epigastrium below ribs. Index marker points towards left	LV/RV size and function Mitral and tricuspid valves Atrial size Pericardial effusion Useful in mechanically ventilated patients
IVC subcostal	Subxiphoid, index marker points to head. Transducer tilts to the left of the patient	IVC size and respiratory variation

- Parasternal long axis (PLAX)
- Parasternal short axis (PSAX)
- Apical four chamber (A4C)
- Subcostal four chamber (SC) and the inferior vena cava (IVC)

7.5 Goals of a Focused Critical Care Echo Examination

A systematic examination using the standard views described above aims to answer the following questions:

- What is the Left Ventricle (LV) size and function?
- What is the Right Ventricle (RV) size and function?
- What is the fluid status (preload), and is there evidence of preload dependence?
- Is there a pericardial effusion? Is the effusion causing cardiac tamponade?

Answering these questions at the bedside provides the clinician with non-invasive information to diagnose and guide treatment for the haemodynamically unstable critically ill patient. Accurate Doppler-based measurements are challenging in the critically ill and often mechanically ventilated patient. Therefore, focus should be placed in a systematic acquisition of good quality 2D images. Any abnormality should be confirmed in at least two windows.

Table 7.3 Normal left ventricle end-diastolic diameter (LVEDD) dimensions

	Male	Female
Normal (mm)	42–59	39–53
Mild (mm)	60–63	54–57
Moderate (mm)	64–68	58–61
Severe (mm)	≥69	≥62

7.5.1 Left Ventricular Assessment

Accurate analysis of left ventricular size function is an essential first step when evaluating a critically ill patient presenting with shock.

The aim of the echo examination will be to determine if the left ventricle is: (Table 7.3)

- Small
- Normal size
- Dilated: mild, moderate or severe

The LV diameter is best measured in the PLAX window at the level of the tip of the mitral valve [13]. The left ventricle end-diastolic diameter (LVEDD) is the largest cardiac dimension and should be obtained shortly before systole begins. This corresponds to the beginning of the QRS complex or the frame just after mitral closure.

The following pitfalls should be avoided when measuring LVEDD:

- Measurements should be taken between the endocardial borders, not the pericardium.
- Distance should be measured perpendicular to the long axis of the LV. 2D measurements are preferred over M-mode for this reason.
- Avoid including papillary muscles or chordae in the measurements.

The most commonly used methods for assessment of LV function in the critical care setting are:

- Visual gestalt or ‘eyeballing’
- Ejection fraction (EF)
- Fractional shortening (FS)
- Cardiac output (CO)

7.5.1.1 Visual Gestalt

Estimation of EF is achieved by ‘eyeballing’ the overall size and contractility of the LV. The thickening and inward movement of the LV walls are assessed in 2D images with no formal measurements required. The use of ‘eyeballing’ by intensivists with basic echocardiography training has been found to have a good level of agreement with LV function estimation performed by experienced echocardiographers [14].

Table 7.4 Normal values for ejection fraction (EF)

Normal	>55 %
Mild	45–54 %
Moderate	30–44 %
Severe	<30 %

Visual quantification of LV function can be divided in normal, mild-to-moderate and severe systolic dysfunction.

7.5.1.2 Ejection Fraction

Systolic performance of the LV (stroke volume) is dependent on contractility, preload and afterload. Ideally, a marker of contractility should not be affected by loading conditions (preload) or afterload. EF is less dependent on preload than stroke volume. However, EF is significantly affected by conditions with high afterload. Despite these limitations, EF is widely accepted as a measurement of LV systolic function [15] (Table 7.4).

Ejection fraction is calculated by subtracting the LV end-systolic volume (LVESV) from the end-diastolic volume (LVEDV) and then dividing by LVEDV.

$$\mathrm{EF} = \mathrm{LVEDV} - \mathrm{LVESV} / \mathrm{LVEDV}$$

EF can be calculated using volumes derived from M-mode. Measurements of the LV, LVEDD and LVESD are obtained in the PLAX window by placing the M-mode cursor in a plane that cuts through the septal and posterior walls of the LV just below the tip of the mitral valve leaflets. LVEDD is measured at the onset of the QRS complex, just prior to MV closure. LVESD measurement is timed to the frame with the minimum LV dimension.

EF is then calculated by computer software that uses the Teichholz or Quinones formulas. These linear calculations have several pitfalls; thus, linear EF measurements are not recommended for critical care practice (Table 7.4).

The Simpson method uses 2D images and calculates LV volume by the summation of the volumes of a stack of elliptical discs constructed inside the LV endocardial outline. It is recommended as the method of choice by the American and European societies of echocardiography [13].

The endocardial border is traced using the A4C and/or apical two-chamber view, and the software in the ultrasound machine calculates the volume of the chamber. Measurements are taken at end-diastole and end-systole (Fig. 7.2).

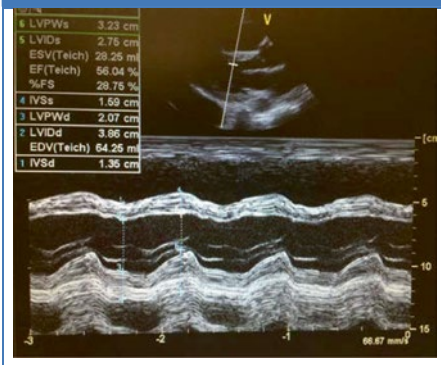
7.5.1.3 Fractional Shortening

Fractional shortening provides a rough estimate of LV function. It is obtained by entering measured LV diameters into the following formula:

$$\mathrm{FS} = (\mathrm{LVEDD} - \mathrm{LVESD}) / \mathrm{LVEDD} \times 100 \quad \text{Normal range: } 25 - 45$$

FS is severely limited by regional wall motion abnormalities and non-global functional alterations that can be missed by the single M-mode plane. This constraint limits the use of FS in the critical care setting.

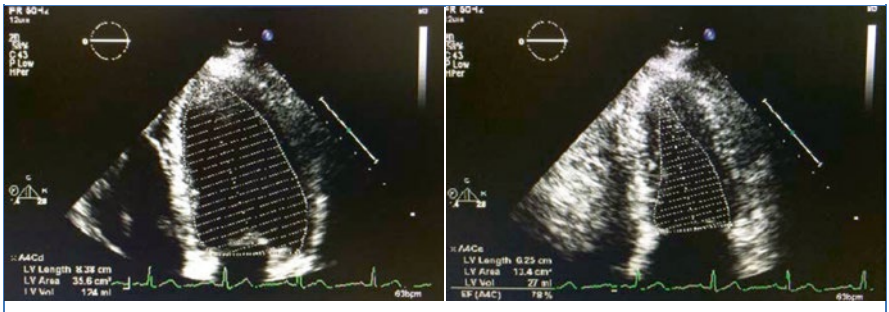
M-mode



Cursor should be perpendicular to LV

- Assumes normal LV geometry
- Affected by regional wall motion abnormalities

2D



Foreshortening of LV can affect measurements

- Requires good image quality to trace endocardial border

Fig. 7.2 Ejection fraction calculation using M-mode and 2D echocardiography

Cardiac Output

Doppler echocardiography is able to obtain non-invasive measurements of cardiac output. The product of stroke volume and heart rate, cardiac output, is widely used in critical care as an indicator of global cardiovascular system function.

The stroke volume, which is the volume of blood ejected by the left ventricle in systole, is received by the proximal ascending aorta. The aorta can be thought of as a cylinder. The volume of the cylinder can be calculated by multiplying the cross-sectional area (CSA) by the height or distance travelled by the fluid in the cylinder. This

measurement is commonly performed at the LVOT, where the CSA is the diameter of the LVOT (cm^2) measured in the PLAX window (Fig. 7.3), and the height is the integral of velocity versus time of the blood passing through the ascending aorta (Fig. 7.4):

$$SV = CSA \times VTI \; .CO = SV \times HR$$

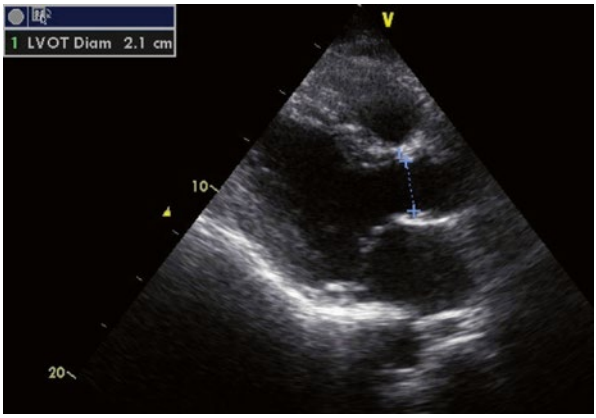


Fig. 7.3 Cardiac output (CO) calculation using Doppler echocardiography. Step 1: LVOT diameter measured in PLAX

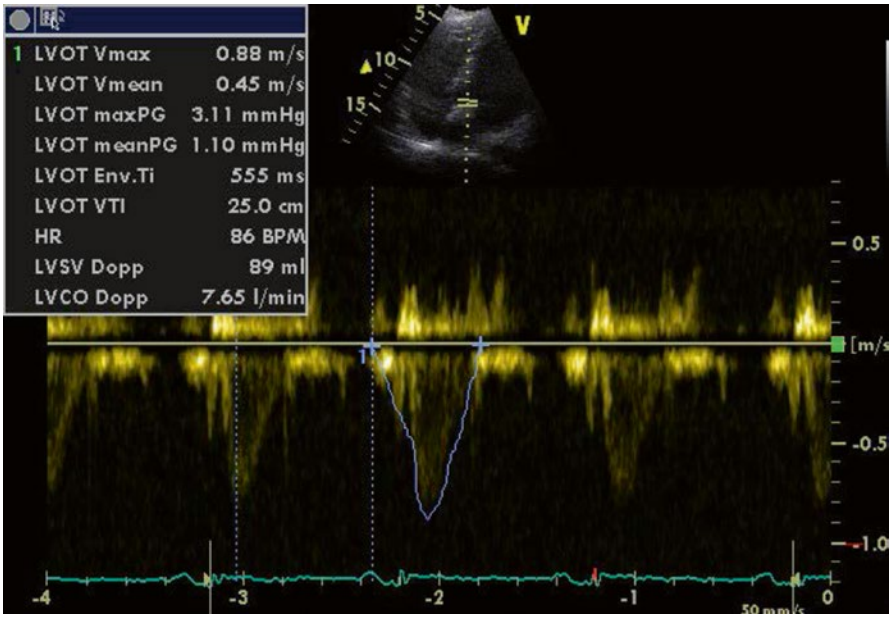


Fig. 7.4 Step 2: Pulsed wave (PW) Doppler signal at the level of the LVOT traced for stroke volume calculation

7.5.2 Assessment of the Right Ventricle

The right ventricle functions as a low-pressure chamber that adapts easily to changes in volume loading but that is less able to tolerate acute increments in afterload. The function of the right ventricle can be directly affected by pathologies frequently encountered in the intensive care such as pulmonary embolism and Adult Respiratory Distress syndrome (ARDS) [16]. Mechanical ventilation and volume status can also impact on the normal function of the RV [17]. Right ventricular dysfunction is directly associated with increased mortality in critically ill patients [18].

7.5.2.1 RV Size and Shape

The size of the right ventricle can be pragmatically assessed by comparing its size with the left ventricle. As a rule of thumb, when viewed in the apical four-chamber window, the right ventricle is said to be enlarged if it appears as large as or larger than the left ventricular cavity.

Conditions that cause right ventricular pressure or volume overload lead to a right ventricular end-diastolic pressure that exceeds that of the left ventricle. This produces a characteristic D-shaped appearance of the LV in a PSAX view.

7.5.2.2 RV Systolic Function

Systolic movement of the right ventricle is characterised primarily by longitudinal displacement of the basal free wall towards the apex. The RV also experiences radial thickening to a lesser degree.

Visual gestalt can be used to describe systolic function of the RV as normal, mildly, moderately and severely reduced. Quantitative assessment of RV systolic function is challenging, and since longitudinal motion is the primary axis of displacement of the RV, measurements quantifying motion in this axis are widely used. Tricuspid Annular Plane Systolic Excursion (TAPSE) is an easy-to-perform method that has been included in the international guidelines for RV assessment [19].

TAPSE quantifies longitudinal motion of the tricuspid annulus and is measured by placing the M-mode cursor in the lateral tricuspid annulus, using the apical four-chamber view. The distance travelled by the annulus from the end of diastole to the end of systole is measured with a calliper. A TAPSE value of $\geq$1.6 cm is considered normal (Fig. 7.5).

7.5.2.3 Pulmonary Artery Pressure

Echocardiography can provide the critical care physician with non-invasive estimation pressures in the pulmonary artery (PAP). Measuring the velocity of a tricuspid regurgitant jet and applying the values to the modified Bernoulli equation can produce an estimate of the PAP:

$$\text{PAPs} = \text{RVSP} = \left(4\text{TRV}^2\right) + \text{RAP}$$

PAPs = Systolic pulmonary artery pressure
RVSP = Right ventricular systolic pressure

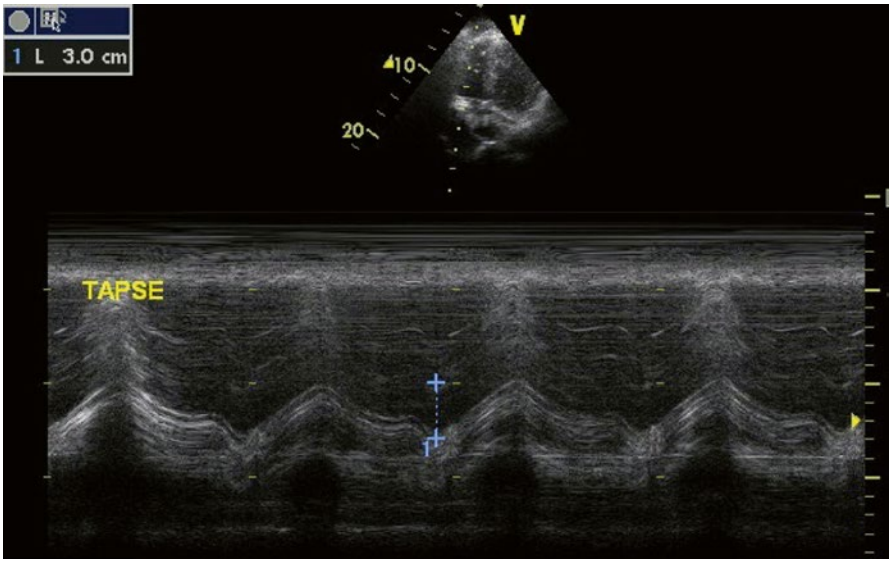


Fig. 7.5 Tricuspid annular plane systolic excursion (TAPSE) determination using M-mode in the apical four-chamber view

TRV = Tricuspid regurgitation velocity
RAP = Right atrial pressure

The apical four-chamber window is most commonly used for obtaining Doppler measurements of the tricuspid valve velocities. Mechanical ventilation and difficulty in positioning critically ill patients might obscure this view. The subcostal view can be used as an alternative.

7.6 Volume Status and Preload Dependence Assessment

Assessment of the volume status is crucial for the appropriate diagnosis and management of the patient presenting with haemodynamic instability. The identification of the patient in shock that will benefit from increasing preload is the mainstay of goal-directed resuscitation algorithms in patients presenting with sepsis [20] or following major surgery [21]. Equally important is the identification of patients who will not benefit or may even come to harm from inappropriate volume expansion; a positive fluid balance has been linked with worse outcomes in patients with sepsis [22] and ARDS [23].

Commonly used parameters to assess volume status in the ICU are inferior vena cava (IVC) diameter, left ventricular size (LV end-diastolic area) and right heart chambers size. Assessment of preload dependence is performed by predicting or evaluating response to a fluid challenge. IVC diameter respiratory variation, peak flow velocity on the left ventricular outflow tract (LVOT) and cardiac output estimation can be used to assess preload dependence.

7.6.1 IVC Diameter

The IVC diameter can be measured as it enters the right atrium, in 2D or M-mode echo, using a modified subcostal view. The measurement should be taken 1 cm caudal to the junction of the first hepatic vein with the IVC (Fig. 7.6).

IVC values and diameter changes with respiration have been used to estimate central venous pressure [24]. However, there is evidence that CVP is a poor indicator of volume status and predictor of fluid responsiveness [25]. IVC size is also affected by mechanical ventilation, which further limits its usefulness in the critically ill patient [26].

Evidence suggests that small IVC sizes (<1.2 cm) are consistently present in hypovolaemic, compared to euvolaemic patients [27]. Conversely, high values of CVP are increasingly likely if IVC diameter values exceed 2 cm [26].

7.6.2 LV and RV Volume Assessment

Measurement of cardiac chambers at end of diastole can be used for estimating the left ventricular end diastolic volume, as previously described.

Using end diastolic dimensions as indicators or volume status are limited by the quality of the images obtained and ventricular systolic function.

However, severe hypovolaemia is very likely when complete obliteration of the left ventricular cavity is seen during systole. This is also known as the 'kissing ventricles' sign.

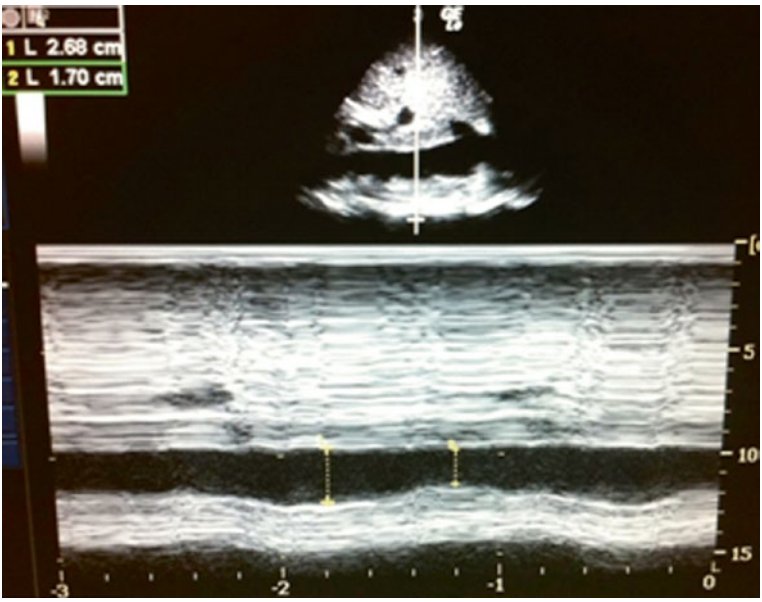


Fig. 7.6 Inferior vena cava (IVC) M-mode. Modified subcostal window

Likewise, a small hyperkinetic right ventricle can also be an indicator of hypovolaemia, if found in a patient with shock.

7.6.3 IVC Respiratory Variation

The IVC is susceptible to changes in intrathoracic pressure and experiences cyclic size variation during either spontaneous or mechanical breathing. Dynamic indexes of IVC size variation have been developed in an attempt to overcome the limitations of static IVC diameter measurements as predictors of volume status and fluid responsiveness.

The inferior vena cava distensibility index (IVC_{DI}) can be used to assess preload dependence in mechanically ventilated patients.

$$IVC_{DI} = \left(\max IVCd - Min\ IVCd / Min\ IVCd\right) \times 100\,\%$$

IVC_{DI} = IVC distensibility index
Max IVCd = Maximum IVC diameter
Min IVCd = Minimum IV diameter

A study of septic patients found that they were likely to be fluid-responsive if the IVC_{DI} value exceeded 18 % [28].

Delta IVC (ΔIVC) is another index that has been found to be useful in detecting fluid responsiveness in patients with septic shock [29]. ΔIVC is obtained by dividing the difference between the maximum and minimum IVC diameters by the mean of the two diameters. ΔIVC of 12 % or more identified patients that was likely to respond to intravascular volume expansion.

A recent meta-analysis including eight studies that looked at the usefulness of IVC diameter variation in prediction of fluid responsiveness concluded that IVC indexes are of value in identifying patients that are likely to be fluid-responsive [30].

This study highlighted that IVC indexes were particularly useful in patients on controlled mechanical ventilation and those resuscitated with colloids. Included studies however used tidal volumes exceeding 8 mL/kg, which limit their applicability in the era of lung-protective ventilation.

7.6.3.1 The IVC Collapsibility Index (IVC_C)

$$IVC_C = \left(Dmax - Dmin\right) / Dmax$$

IVC_C is a widely used index that was first validated in spontaneously breathing patients with heart failure, undergoing slow continuous ultrafiltration (SCUF) [31].

This study found that only those patients that reached an IVC_C >30 % experienced hypotension. A similar study, performed in spontaneously breathing patients with acute circulatory failure, found that high IVC_C values (>40 %) were present in fluid-responsive patients [32].

7.6.3.2 Velocity Time Index Variation (VTI)

The velocity time index (VTI) of flow through the left ventricular outflow tract (LVOT) and its variation with respiration can also be used for the assessment of preload dependence.

VTI value is obtained by placing a pulse-wave Doppler (PWD) sample volume in the LVOT just below the aortic valve. The obtained waveform is traced, and a VTI value in centimetres is obtained. VTI waveforms are obtained for three or four respiratory cycles. Measurements of VTI are then obtained for the largest and smallest waveforms observed during a single respiratory cycle. VTI variation (ΔVTI) is then calculated as follows:

$$\Delta VTi = VTImax - VTImin / VTI\,mean$$

A study of mechanically ventilated septic shock patients found that a ΔVTI value of >12 % discriminated between responders and non-responders to volume expansion with a sensitivity of 100 % and specificity of 89 % [33]. ΔVTI is able to predict fluid responsiveness even when a small volume of fluid or 'mini' fluid challenge of 100 mL is administered. In a study performed in mechanically ventilated patients with acute circulatory failure, a 10 % increase in VTI following a 100 mL rapid bolus administration accurately predicted fluid responsiveness to further larger volume of fluids [34]

7.7 Evaluation of Pericardium and Tamponade

The diagnosis of pericardial tamponade requires for fluid to be present in the pericardial space and for this fluid to cause a haemodynamic effect.

The basic echo window's subcostal four-chamber, PLAX, PSAX and apical four-chamber views are useful for visualisation of pericardial fluid. Effusions can be quantified as small (<0.5 cm), moderate (0.5–2 cm) and large (>2 cm) [35]. The size of the effusion is not the only factor determining the physiological effect of the fluid accumulated; the rate of accumulation is equally or more important.

The diagnosis of tamponade depends upon the demonstration of 'tamponade physiology', which occurs when the pressure inside the pericardial space surpasses that of the cardiac chambers impairing normal filling [36]. Typical 2D echocardiographic characteristics of tamponade are RA systolic collapse, RV diastolic collapse, severe fixed dilatation of the IVC and variations of the RV and LV size with respiration.

7.8 Echocardiographic Approach to the Patient with Shock

Echocardiography can play an important role as a diagnostic tool and haemodynamic monitor in the patient presenting with haemodynamic instability. There is wide agreement in recommending focused echocardiography in the early assessment of a patient presenting with shock [37].

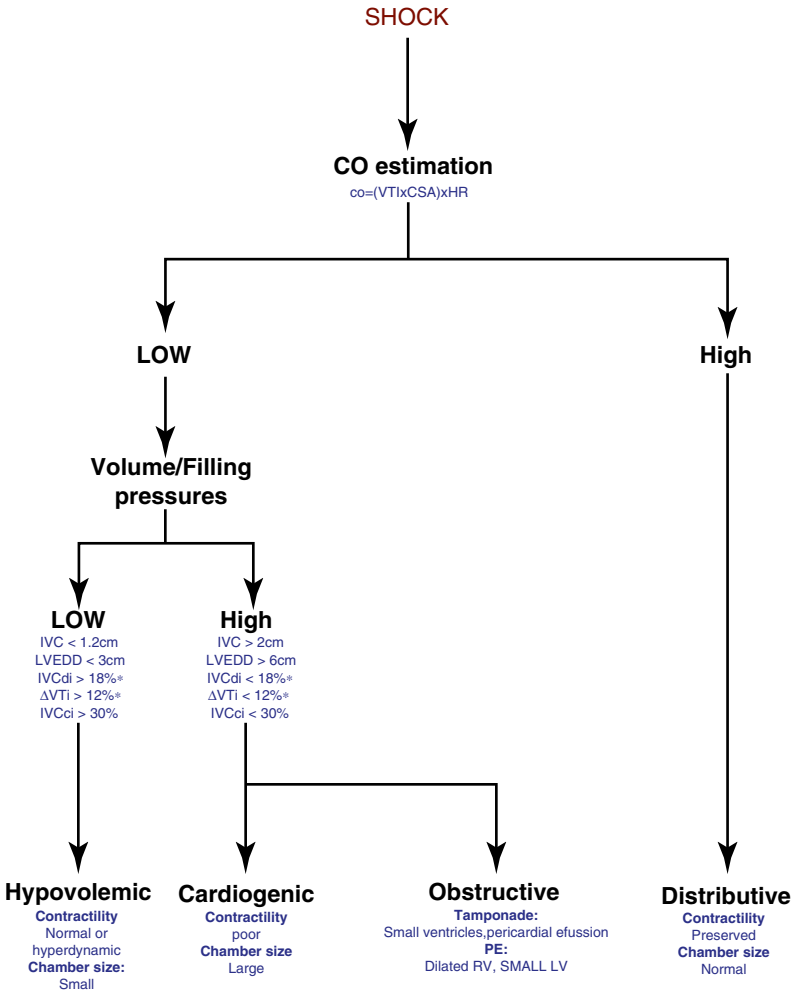


Fig. 7.7 Echocardiographic approach to the patient with shock algorithm. *CO* cardiac output, *VTI* velocity time index at the *LVOT* left ventricle outflow tract, *CSA* cross-sectional area of the LVOT, *IVC* inferior vena cava, *LVEDD* left ventricle end-diastolic diameter, *IVCdi* IVC distensibility index, *ΔVTi* VTI variability index, *IVCci* IVC collapsibility index (*Mechanically ventilated patients only)

Establishing rapidly the type and cause of shock allows for instigation of prompt and targeted treatment. Echocardiography supplements, in a non-invasive manner, medical history, clinical examination and investigations.

Systematic estimation of volume status, systolic function and observation of chamber obstruction can complete the clinical picture in the diagnosis of shock.

There are four steps in the echocardiographic assessment of the patient in shock:

Step 1: Estimation of the cardiac output by obtaining stroke volume through the Doppler examination of the LVOT flow signal.
Step 2: Assessment of volume status and filling pressures, which can be achieved by examining the size and respiratory variation indexes of the IVC. Variability in VTI in the LVOT can also be used. Cardiac chamber size also provides useful information regarding volume status.
Step 3: Assessment of contractility
Step 4: Examination of pericardial space to rule out pericardial effusion.

Bringing all these steps together in an algorithm (Fig. 7.7) allows for echocardiographic diagnosis of the patient with haemodynamic instability.

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The Role of Lung Ultrasound on the Daily Assessment of the Critically Ill Patient

8

Nektaria Xirouchaki and Dimitrios Georgopoulos

Summary of Abbreviations

ARDS	Adult respiratory distress syndrome
LU	Lung ultrasound
PEEP	Positive end-expiratory pressure

8.1 Introduction

The first lung ultrasound (LU) pattern, obtained from a patient with pleural effusion, was described by Pell in 1964. Three years later, Joyner et al. [1] published the first study which described the accuracy and reliability of LU in the diagnosis of pleural fluid. Thereafter, for several years, the use of LU was limited only to the detection of pleural effusion. This has drastically changed in the last decade. Nowadays, LU has emerged as a powerful, non-invasive, easily repeatable bedside diagnostic tool, and is increasingly used in critically ill patients [2–4]. Studies have shown that in these patients, LU has a high diagnostic accuracy in identifying pneumothorax, consolidation/atelectasis, interstitial syndromes (i.e. pulmonary oedema of cardiogenic or non-cardiogenic origin), pleural effusion, and, on the appropriate clinical grounds, it may help in the diagnosis of pneumonia. Indeed, LU may be considered an alternative to thoracic computed tomography (CT) scan when identifying these

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_8

pathological conditions which are commonly encountered in critically ill patients (Fig. 8.1) [2, 3].

As a result, LU is likely to have a significant impact on clinical decision-making and therapeutic management of these patients [3, 5]. LU may also be used to assess and monitor lung aeration, which is of particular importance in patients with acute respiratory distress syndrome. This application may guide the titration of positive end-expiratory airway pressure (PEEP) and may serve as a safeguard against excessive fluid loading in critically ill patients [6]. Finally, it has been shown that ultrasound may be used to measure the thickening fraction of the diaphragm during tidal breathing, which is useful as a non-invasive estimation of the work of breathing in critically ill patients [7].

Despite the proven diagnostic ability of LU and its influence on decision-making and therapeutic management, there are significant barriers to the widespread use of this pragmatic, non-invasive bedside tool. The fact that the interpretation of LU findings is heavily dependent on operator experience represents one important limitation. In addition, LU may not identify with accuracy, deep pulmonary lesions.

The aim of this chapter is to introduce the ultrasonography imaging of the lungs and pleura, and the main LU findings associated with basic respiratory disorders in critically ill patients (Table 8.1).

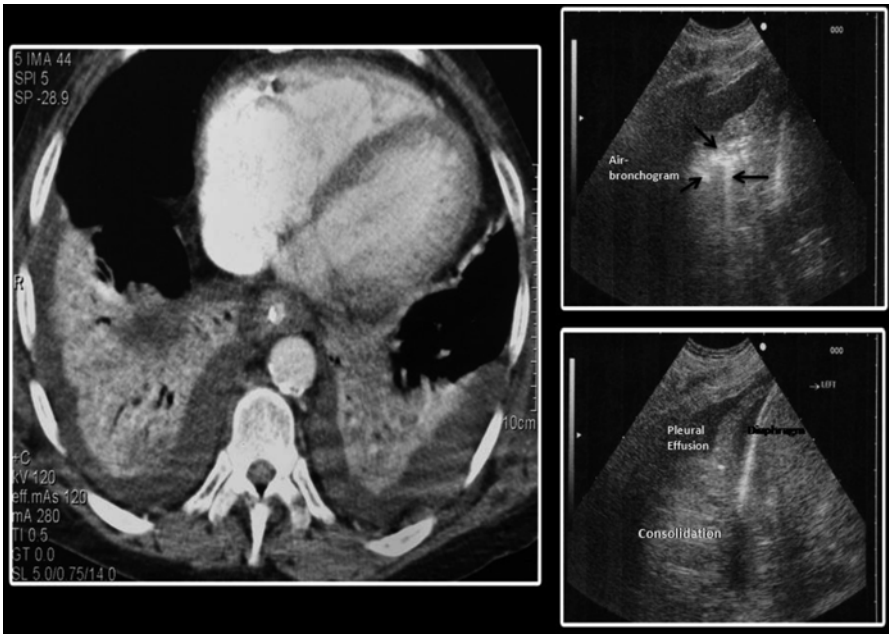

Fig. 8.1 *Left*: Multiple detector computed tomography after intravenous contrast arterial revealed bilateral consolidations with air bronchogram (*arrows*), associated with pleural effusions. *Right*: Lung ultrasound longitudinal scan at the lower lateral regions. The main ultrasound features included bilateral consolidations with air bronchogram (*arrows*) and pleural effusions (From Georgopoulos et al. [4])

Table 8.1 The use of lung ultrasound in various lung and pleural pathologic conditions

Lung parenchyma abnormalities
1. Consolidation
(a) Atelectasis
(b) Pneumonia
(c) Lung contusion
2. Interstitial syndrome
(a) Congestive heart failure
(b) Acute respiratory distress syndrome
(c) Lung contusion
(d) Pneumonia
(e) Interstitial lung diseases
(f) Evaluation of lung congestion
(g) PEEP titration and lung recruitment in ARDS patients
3. Lung overdistention
4. Pulmonary embolism
Pleural diseases
1. Pneumothorax
2. Pleural effusion
3. Evaluation of diaphragm contraction – paralysis
4. Diaphragm ultrasound as a predictor of successful weaning

8.2 Equipment

Lung ultrasonography can be performed using any commercially available 2D scanner. Today, portable machines are lightweight, relatively inexpensive and can easily be used at the bedside. High-frequency transducers provide excellent resolution, but do not visualise deep structures (poor penetration). Both the microconvex 3–8 MHz probe and the high-frequency linear probe (8–12.5 MHz) are suitable. The use of the microconvex transducer facilitates semi-posterior analyses with minimal patient mobilisation. The probe depth should range between 60 and 140 mm, and, in an effort to reduce the natural artefacts, tissue harmonics are preferable. Colour Doppler and power Doppler can be helpful for the detection of blood flow signals within consolidated areas [3, 8].

8.3 Ultrasound Waves and Lung Interaction

It is well known that there is poor interaction between the air-filled lungs and the ultrasound beam [9]. Ultrasound, in general, is reflected at tissues, and the amount of reflected ultrasound is associated with the relative change in acoustic impedance [10]. In the case of the normal lung, the ultrasound beam meets the aerated lung (low impedance 0.004 Rayl, and no acoustic mismatch). On the other hand, in the presence of extravascular lung water, the ultrasound beam is reflected at the interlobular septa,

thickened by oedema (in this case, high impedance and high acoustic mismatch). When the lung is associated with complete loss of aeration, LU displays a tissue-like pattern similar to the liver (high impedance 1.65 Rayl, high-speed sound velocity).

8.4 Examination Protocols

There are, in essence, two examination LU protocols. In the first protocol, the lungs are divided into 12 regions [2]. The anterior surface of each lung is defined by clavicle, parasternal, anterior axillary line, and the diaphragm is divided into two areas, upper and lower. The lateral surface is defined by the anterior and posterior axillary lines and divided into an upper and lower area. Finally, the posterior lung surface is defined by the posterior axillary and the paravertebral lines and divided into an upper and lower area. The lung apex is scanned from the supraclavicular space [3]. In the second protocol, which is simpler, the operator examines the anterior and lateral areas of each hemithorax from the second to the fourth or fifth intercostal spaces, and from parasternal to the axillary line [11].

8.5 Lung Ultrasound Imaging

8.5.1 The Normal Lung Pattern

The probe is placed vertically over the intercostal space. The resultant image depicts the superior and inferior ribs, their acoustic shade, and the pleural line, 0.5 cm from an imaginary line connecting the ribs [2, 12]. The pleural line corresponds to the visceral pleura and represents the lung surface. Lines parallel to the pleural line are referred to as A-lines. These represent reverberation artefacts with constant location. Apart of these static signs, the normal lung generates a dynamic sign known as ‘lung sliding’. The sliding movement of the visceral pleura towards the parietal pleura during the respiratory cycle characterises it. In time-motion mode, the normal lung pattern is illustrated by the ‘seashore sign’ (Fig. 8.2) [12]. The latter is characterised by the chest wall layers over the pleural line and a granular pattern below it. In many cases, pleura act as a mirror producing the mirror effect [13].

8.5.2 Pathological Conditions: Lung Parenchyma

8.5.2.1 Atelectasis/Consolidation

Atelectasis/consolidation is associated by the complete loss of the lung aeration. LU displays a tissue-like structure pattern, similar to the liver [14, 15]. It is associated with (1) abolition of the lung sliding and dynamic diaphragmatic movement and (2) the presence of static air bronchogram within the atelectasis/consolidation. In critically ill patients, this pathology is usually also associated with pleural effusion. In this case, particularly in the dependent lung regions, the compressed lung floats within the effusion, a LU finding which is very common in critically ill

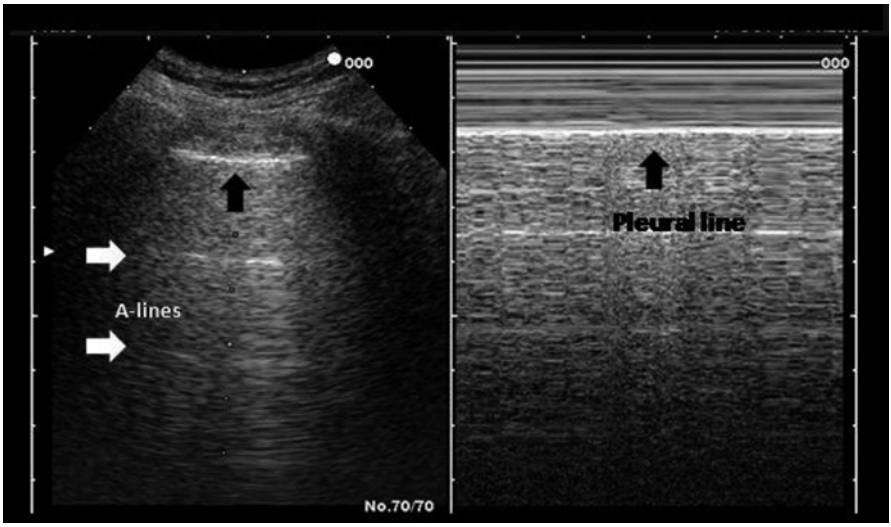

Fig. 8.2 The normal lung pattern. Pleural line is shown by *black arrows*. At the right of the screen appears the 'seashore sign'. It is characterised by the chest wall layers over the pleural line and a granular pattern below it. Parallel lines to the pleural line (*white arrows*) are reverberation artefacts known as A-lines

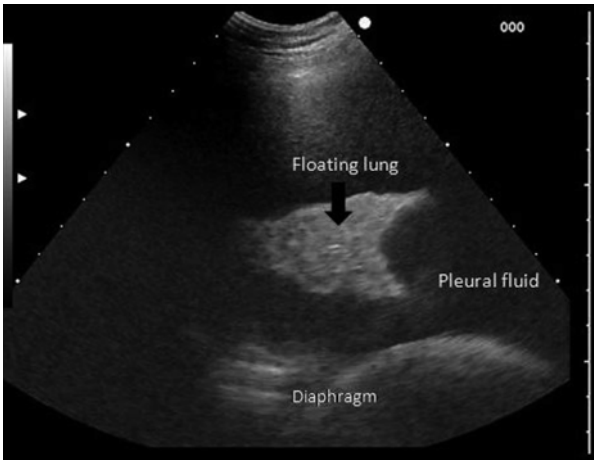

Fig. 8.3 Atelectatic lower lobe floating into the pleural fluid (black anechoic area)

mechanically ventilated patients (Fig. 8.3) [5]. The static air bronchogram is caused by entrapped air inside a lung area that is no longer aerated, thus creating hyperechoic punctiform images (artefacts) [16].

8.5.2.2 Interstitial Syndrome

Interstitial syndrome is characterised by the presence of multiple B-lines. B-lines are well-defined hyperechoic comet-tail artefacts, arising from the pleural line and extending into the far field [17]. They move according to the lung-sliding movement, erasing the A-lines. B-lines may arise from thickened pleura due to the

accumulation of fluid (oedema) or in interstitial lung diseases, from fibrosis-thickened subpleural septa. The distance between B-lines may help to differentiate between these two mechanisms; the presence of B-lines, 7 ± 1 mm apart (B7-lines), is consistent with the thickening of the interlobular septa, whereas B-lines 3 ± 1 mm apart (B3-lines) indicate oedema and correspond to ground-glass pattern in CT scan. The former pattern is resistant to diuretic therapy, while the latter may respond to therapy towards the cause of pulmonary oedema (i.e. diuretics, dialysis, PEEP), even within minutes or hours [10, 18, 19]. White lung is defined as completely white echographic lung fields, with coalescent B-lines and no horizontal reverberation (Fig. 8.4). A recent study examined the ability of the bedside LU to quantify the PEEP-induced lung recruitment. This study clearly shows that using LU for PEEP titration in ARDS patients is accurate enough and has the advantage of being non-invasive and easily performed at the bedside [6].

8.5.2.3 Pneumonia

Echographic lung imaging from standard windows allows the evaluation of pneumonia, since most pneumonias in critically ill reach the pleura [15, 20, 21]. The LU signs that support the diagnosis of pneumonia are (1) bilateral or local B-lines pattern, (2) the presence of anterior lung consolidation with irregular boundaries, (3) the existence of vascular flow within the infected area, (4) the presence of pleural effusion and (5) the dynamic air bronchogram [16]. Dynamic air bronchogram is illustrated by linear or punctiform hyperechoic artefacts within a consolidation with dynamic movement according to the respiratory cycle, representing the air moving into the bronchial tree (Fig. 8.5). LU may track the response to therapy in critically ill patients with pneumonia. Bouhemad et al. have shown that lung re-aeration can be accurately estimated with bedside LU in patients with ventilator-associated pneumonia treated by antibiotics [22].

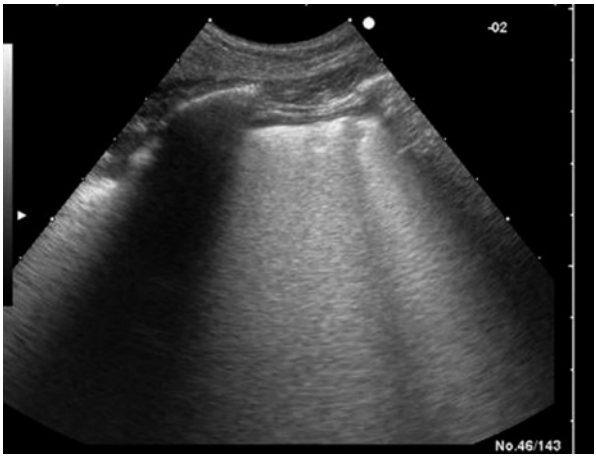

Fig. 8.4 White lung in a patient with severe ARDS. Notice the white echographic lung fields and no horizontal reverberation (no A-lines)

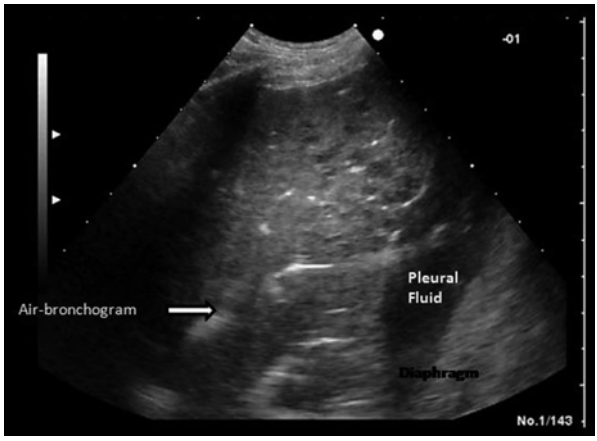

Fig. 8.5 Lower lobe consolidation due to pneumonia associated with small pleural effusion. Air bronchogram can be recognised inside the pathological area. The diaphragm displays irregular shape due to the inflammatory process

8.5.2.4 Pulmonary Embolism

The value of LU in the diagnosis of pulmonary embolism remains controversial [20, 23]. Although LU is not the imaging method of choice for the diagnosis, on appropriate clinical grounds, it may assist the diagnostic workup. Particularly, two or more triangular homogeneous pleural-based lesions, well demarcated and located in the posterior basal segments of the lung in a patient with clinical picture compatible with pulmonary embolism, strongly suggest the diagnosis. Nevertheless, a negative LU result does not rule out a pulmonary embolism [23].

8.5.2.5 Overdistention

Overdistention mainly caused by increased intrathoracic pressures is difficult to recognise using LU and requires a highly experienced operator. It is suspected when LU displays parallel reverberations without lung-sliding abolition. In addition, remarkable loss of vertical reverberation in regions where they were observed previously also favours the diagnosis of overdistention [5, 6].

8.5.3 Pathological Conditions: Pleura

8.5.3.1 Pneumothorax

The LU diagnosis of pneumothorax is challenging, and the operator should be skilled in the interpretation of LU findings in order to support or exclude this condition. Examination of anterior chest wall often is sufficient, since air rises to the anterior thoracic wall in the supine critically ill patient. When LU is performed for suspicion of pneumothorax, the operator should search for findings that support or exclude this diagnosis. Findings that support the diagnosis of pneumothorax are as follows: (1) Motionless pleural line with horizontal reverberations. However, this finding is not specific since massive atelectasis, pulmonary contusion, ARDS and pleural adhesions may cause a motionless pleural line [24, 25]. (2) Time-motion mode displays a strict pattern of parallel lines, suggesting complete absence of

structures below the pleural line (stratosphere sign) [26]. (3) The presence of lung point. Lung point is a sign, specific for pneumothorax, and is defined as a change from lung patterns to pneumothorax patterns, and vice versa, depending on the respiratory phase (inspiratory/expiratory) (Fig. 8.6) [27]. Two signs usually exclude the diagnosis of pneumothorax. First, the presence of B-lines, since this finding necessitates lung parenchyma, and second, the presence of lung pulse defined as the transmission of heart beats through a consolidated lung [25].

8.5.3.2 Pleural Effusion

LU is the gold standard imaging method for identification of pleural effusion [28]. Pleural effusion is determined as a hypoechoic or echoic structure, containing isoechoic particles or septations in inflammatory pleural diseases (Fig. 8.7).

When the lung is compressed by pleural fluid, the lower lobe is collapsed and floats in the pleural effusion. LU may in some cases differentiate between transudative or exudative pleural effusion [12, 28]. Transudates usually have an echo-free pattern, whereas exudates contain fibrous strings and mobile or immobile septations with encapsulated liquid. Colour Doppler is also useful for pleural effusion differentiation [3, 8]. LU may also be used to guide thoracentesis and to estimate the fluid volume. Estimation of pleural fluid volume is most accurate for effusions between 150 and 1000 mL [29, 30]. A simple formula for effusions larger than 150 mL is Volume (mL) = 20 × interpleural distance (mm) [31].

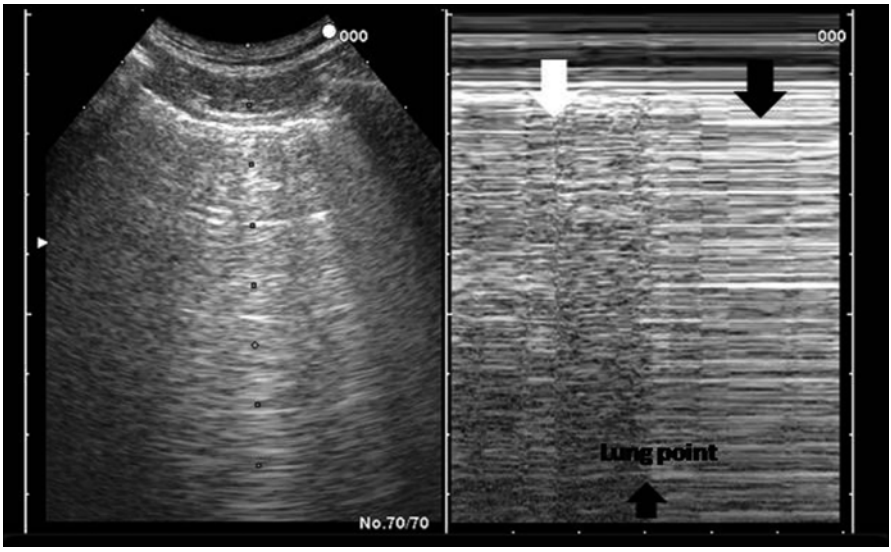

Fig. 8.6 Illustration of the lung point, a specific sign for pneumothorax in M-mode, characterised by a line illustrating the point of transition between the seashore sign (presence of lung, *white arrow*) and stratosphere sign (absence of lung, *black arrow*), caused by respiratory movements (inspiration/expiration)

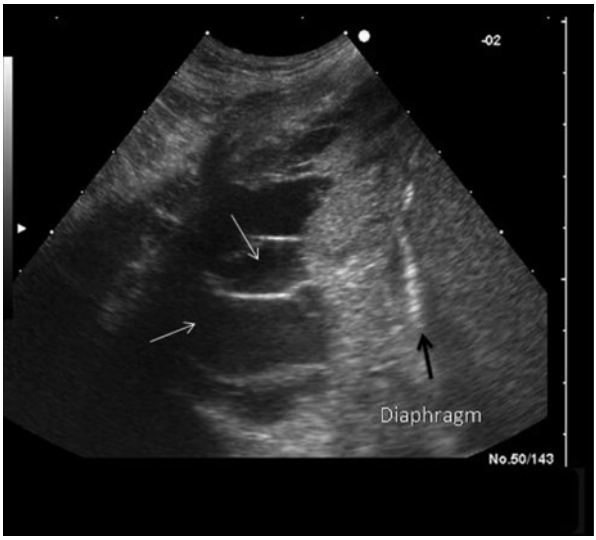

Fig. 8.7 Complicated pleural effusion with pockets (*white arrows*), tissue and diaphragms. The irregular diaphragmatic shape (*black arrow*) is due to inflammation

8.5.4 Evaluation of the Diaphragm

The probe is placed immediately below the right or left costal margin between the midclavicular line and the right or left anterior axillary line, and is directed medially, cranially and dorsally; so, the ultrasound beam reaches perpendicularly the posterior third of the corresponding hemidiaphragm. In the M-mode, the diaphragmatic excursion (displacement, cm), the speed of diaphragmatic contraction (slope, cm/s), and the inspiratory (ti, s) and expiratory time (te, s) can be easily measured. The values of diaphragmatic excursion in healthy individuals were reported to be 1.8 ± 0.3 cm for males and 1.6 ± 0.3 cm for females in quiet breathing; 2.9 ± 0.6 cm for males and 2.6 ± 0.5 cm for females during voluntary sniffing; and 7.7 ± 1.1 cm and 5.7 ± 1 cm, respectively,during deep breathing [32, 33]. Obviously, LU can easily diagnose the diaphragmatic paralysis. In addition, it has recently been shown that LU may be used to measure the thickening fraction of the diaphragm during tidal breathing, which is useful as a non-invasive estimation of the work of breathing in critically ill patients. Finally, the thickening fraction of the diaphragm may be useful to predict successful weaning from mechanical ventilation [34].

Conclusion

LU is a powerful imaging technique for the evaluation of the respiratory system at the bedside, and there is significant evidence in the literature supporting the pivotal role of this method in the management of critically ill patients. LU has a high diagnostic accuracy in identifying the most common pathological conditions of respiratory system in these patients, as well as to track response to various therapeutic interventions. Intensivists must be familiar with this technique, since the ultrasound examination of the lung is one of the required elements to achieve competence in general critical care ultrasound.

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Acute Liver Failure: Diagnosis and Management for the General Intensive Care

9

Behrad Baharlo

Summary of Abbreviations

AoCLD	Acute-on-chronic liver disease
HELLP	Haemolysis, elevated liver enzymes, low platelet count
ICP	Intracranial pressure
MHRA	Medicines and healthcare products regulatory agency
PEEP	Positive end expiratory pressure

9.1 Introduction

Acute liver failure is a rare condition, resulting from a rapid decline in hepatic function with potentially life threatening sequelae. Incidence in the UK is estimated between 1 and 8 per million population [1] accounting for approximately 400 new cases per year. Despite advances in supportive management and liver transplantation, the only curative treatment, 1-year survival is around 60 % [2, 3].

Whilst definitions of acute liver failure have been diverse and evolving [4], it remains a syndrome featuring jaundice, coagulopathy, encephalopathy and multiorgan dysfunction. The presence of hepatic encephalopathy (of any grade) is the mandatory clinical feature in establishing the diagnosis of acute liver failure (Table 9.1). Jaundice, coagulopathy and other organ dysfunction (typically but not limited to renal) may or may not be present to varying extents.

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_9

Table 9.1 Grading of severity of hepatic encephalopathy

I	Slow mental function
II	Inappropriate behaviour
III	Daytime somnolence
IV	Coma

Table 9.2 Characteristics of subgroups of patients with acute liver failure as defined by O'Grady [6]

	Hyperacute	Acute	Subacute
Encephalopathy	Yes	Yes	Yes
Jaundice → encephalopathy	Within 7 days	Between 8 and 28 days	Between 29 and 72 days

Table 9.3 Aetiology of patients with acute liver failure and interval between appearance of jaundice and development of encephalopathy

Hyperacute	Acute	Subacute
Acetaminophen overdose	Hepatitis A-E	Seronegative hepatitis (Non A-E)
Viral hepatitis	Autoimmune hepatitis	
HELLP	Budd-Chiari	
Ischaemic hepatitis	Other idiosyncratic drug reactions	
	Viral hepatitis	
	Wilson's disease	

Adapted from O'Grady [6]

The differentiation between hepatic encephalopathy and other causes of altered mental state whilst difficult has to be made. Furthermore, acute liver failure must not be confused with an acute decompensation of chronic liver disease (AoCLD), which is discussed later in this chapter.

Originally the term 'fulminant hepatic failure' was used (as part of a surveillance study in the USA of liver damage after halothane anaesthesia) to describe 'a severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of pre-existing liver disease [5].

The observation of late-onset hepatic failure where encephalopathy appears between 8 and 26 weeks after the onset of symptoms led to the redefinition that became known as the King's classification [6]. Here, the time interval between jaundice specifically rather than symptoms, to onset of encephalopathy defined the distinction between hyperacute, acute and subacute liver failure [6] (Table 9.2).

Common aetiologies of acute liver failure are listed in Table 9.3 according to the time of onset of acute liver failure (Table 9.3). The significance of the King's classification is not only in definition but also providing inference about likely outcome, aetiology and implication on management [7]. The data upon which the King's classification is based also forms the basis of the King's College criteria for liver transplantation, which remains in use to this day [7].

Based on the above, another widely accepted definition of acute liver failure is that of a coagulopathy (INR > 1.5) and any degree of encephalopathy in a patient without pre-existing cirrhosis and with illness duration of <26 weeks. However,

patients with vertically acquired Hepatitis B, Wilson's disease and Autoimmune hepatitis are included despite the possibility of pre-existing cirrhosis, so long as their disease has been recognised for <26 weeks.

9.2 Initial Management

Once a diagnosis of acute liver failure is suspected or established, patients should undergo concurrent investigation and treatment with the initial aim being to identify the aetiology and institute any disease specific therapy, which may be appropriate. Depending on the initial presentation, resuscitative measures may have to be instigated simultaneously. An appreciation of factors that make for a poor prognosis also enables the early identification of patients who are likely to fail supportive medical management and require liver transplantation.

Clearly not every patient where a diagnosis of acute liver failure is made or suspected will have a metabolic derangement that would warrant intensive care unit (ICU) admission or indeed be referred to ICU. For example, patients with subacute failure may remain for long periods with low-grade encephalopathy on a medical ward.

However, it is important to bear in mind that even in the presence of hepatic regeneration patients will succumb to complications such as sepsis or multi-organ failure and will need a close level of monitoring. Furthermore, patients presenting with hyperacute or acute liver failure can rapidly progress to multi-organ failure.

As a result it is recommended that, a low threshold for admission to critical care be adopted, especially until the aetiology is established.

The main indications for ICU referral and admission are as follows [3, 8]:

- Hyperacute or acute presentation
- Any degree of encephalopathy
- Renal failure
- Metabolic derangement

The ICU clinician should anticipate the severity of presentation and likelihood of supportive and medical therapy failing despite optimal care. The most widely accepted prognostic tool in acute liver failure is the King's College criteria.

The King's College criteria were originally used to predict survival without liver transplantation. It is now used to refer patients to a specialist liver unit and select potential liver transplant recipients.

The King's College criteria differ between paracetamol and non-paracetamol causes. It has a good specificity (82–92 %) but limited sensitivity (68 %). Its positive predictive value for ICU death without transplantation is 0.98 and the negative predictive value is 0.82 [7] (Tables 9.4 and 9.5).

The use of arterial lactate is used to improve the sensitivity of the King's Criteria in the context of paracetamol-induced liver failure [9]. Lactate concentrations of >3.5 mmol/L on admission and >3.0 mmol/L after adequate fluid resuscitation, when used in combination had similar predictive ability as the King's criteria but

Table 9.4 Criteria for referral to specialist liver unit following paracetamol ingestion (post resuscitation) [3]

Day 2	Day 3	Day 4
Arterial ph < 7.3	Arterial ph < 7.3	INR > 6 or PT > 100
INR > 3.0 or PT > 50s	INR > 4.4 or PT > 75 s	Progressive rise in PT
Oliguria	Oliguria	Oliguria
Creatinine > 200 μmol/L	Creatinine > 200 μmol/L	Creatinine > 300 μmol/L
Encephalopathy	Encephalopathy	Encephalopathy
Hypoglycaemia	Severe thrombocytopenia	Severe thrombocytopenia

Table 9.5 Criteria for referral to specialist liver unit for non-paracetamol aetiologies (post resuscitation) [3]

Hyperacute	Acute	Subacute
Encephalopathy	Encephalopathy	Encephalopathy
Hypoglycaemia	Hypoglycaemia	Hypoglycaemia (rare)
PT > 30s	PT > 30s	PT > 20S
INR > 2.0	INR > 2.0	INR > 1.5
Renal failure	Renal failure	Renal failure
Hyperpyrexia		Hyponatraemia
		Shrinking liver volume on CT scan

identified non-surviving patients earlier. The use of the post resuscitation lactate increases the sensitivity of the King's criteria to 91 % [9]

All patients with any degree of encephalopathy, with acute liver failure should be referred to a specialist liver unit.

It should be noted that once a decision to transfer a patient with encephalopathy has been made, then sedation and artificial ventilation should be considered for safe transfer. Specifically, good practice advocates sedation and ventilation even in grade I and II encephalopathy. These patients can deteriorate rapidly with potential for associated cardiovascular collapse.

A careful history must be taken including collateral histories from family members. Clinicians in referring hospitals often have a window of opportunity to meticulously enquire for aetiology especially regarding exposure to viral infections and drugs before the onset of encephalopathy. A common reason behind indeterminate aetiologies lies in inadequate history at the time of presentation and this can complicate further management [10], thus the taking of a thorough history in identifying the aetiology cannot be overstated.

Enquiry into recent foreign travel to endemic areas, risk factors for immunosuppression (e.g. immunosuppressant drugs, history of carcinomas and chemotherapy), high-risk sexual activity and medication history including alternative medicines should be made. Intravenous and recreational drug use particularly but not limited to cocaine and amphetamines and the ingestion of poisonous wild mushrooms, usually due to misidentification, should also be excluded.

Questioning of psychiatric history and neurological disorders especially in the context of renal tubular acidosis (especially Fanconi's syndrome) are particularly relevant, indicating Wilson's disease, whilst history of pregnancies, miscarriages and amenorrhea could indicate autoimmune hepatitis or HELLP syndrome. If a Budd-Chiari syndrome is diagnosed, then a search for an underlying cause should be made (to include malignancy, antiphospholipid syndrome, protein S, C and antithrombin III deficiency and factor V Leiden).

It is important to remember that even paracetamol taken within recommended daily doses have been known to cause acute liver failure, thus the potential for inadvertent overdose exists, especially in high risk groups (e.g. anorexia nervosa and alcohol abuse). Particular attention should be paid to interpreting paracetamol levels in these groups and familiarity with guideline updates is advised [11].

A thorough social history is important in lieu of any potential transplant assessment.

A history or clinical stigmata suggesting underlying chronic liver disease should be sought as this would alter management.

Imaging by computerised tomography is useful in cases where there is a history of cancer, if patency of portal vessels is queried or if Budd-Chiari syndrome is suspected. It is also indicated where intracranial hypertension and cerebral oedema is suspected, but clearly the risks in transportation in this cohort of systemically unstable patients needs to be balanced against the potential management benefits of imaging.

Initial laboratory investigations should be extensive to evaluate aetiology and severity of acute liver failure [8]. It is recommended that a full liver screen is requested on first presentation, even if it is intended for the patient to be transferred to a specialist liver unit (Box 9.1). To avoid delays, these results, once known should be communicated to the specialist liver unit to expedite the commencement of any specific aetiology-based therapy or decision for listing for transplantation.

Box 9.1. The Following Investigations Are Recommended as Part of a Complete Acute Liver Failure Aetiology Screen

Haematology	Full blood count, coagulation screen to include prothrombin time, INR, group and save
Biochemistry	Urea and electrolytes, creatinine, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, liver function tests, albumin, amylase, lipase, arterial blood gas, arterial lactate, cearuloplasmin (or uric acid and bilirubin to ALP ratio) βHCG/pregnancy test (females), ammonia
Toxicology	Paracetamol and salicylate levels, toxicology screen
Virology	Anti HAV IgM, Hep BsAg, Hep Bs antibody, anti Hep Bcore IgM, anti Hep E, anti Hep C, Hep C RNA, HSV1 + 2 IgM, VZV, EBV, HIV 1 + 2
Immunology	ANA, anti SMA, ANCA, anti LKMA, immunoglobulin

Adapted from Lee [8]

Causes

The aetiology and incidence of acute liver failure varies worldwide. Overall the incidence is significantly lower in the developed world when compared to developing countries where viral infections (hepatitis A, B and E) are the main aetiologies [12]. In the United States and Western Europe drug induced aetiologies, especially paracetamol predominates, followed by non A-E hepatitis where no cause is found (Table 9.6).

As previously stated, acute liver failure can be diagnosed in a previously well but undiagnosed patient with Wilson's disease, hepatitis B or autoimmune hepatitis where compensated cirrhosis may have been present, provided the disease has been recognised for less than 26 weeks.

9.3 Clinical Features

Acute liver failure results in a systemic inflammatory response and has multisystemic manifestations. Table 9.7 illustrates the clinical features and therapeutic options according to the organ system affected.

9.4 General Management

There are a number of points in the general management of liver failure patients that are relevant irrespective of the underlying aetiology.

Patients with acute liver failure should be managed according to standard best practices on the intensive care unit.

Since serial evaluation of laboratory coagulation variables, like INR and PT, are important elements of prognostic evaluation, the administration of coagulation factors should be avoided except if the patient is bleeding or prior to invasive procedures [12].

Intubation of the trachea is recommended for patients with severe metabolic disturbance refractory to adequate fluid resuscitation and in patients with grade III and IV encephalopathy, typically for airway protection and carbon dioxide control. Propofol

Table 9.6 Common causes of acute liver failure

Viruses	Hepatitis A, Hepatitis B, Hepatitis E, Cytomegalovirus, Epstein–Barr
	Parvovirus, Herpes simplex virus
Drugs	Acetaminophen, other idiosyncratic drug reactions, mushroom ingestion
Ischaemic	Hypoxic hepatitis[a], Budd-Chiari
Other	Wilson's disease, acute liver failure of pregnancy/HELLP, neoplastic, unknown aetiology

[a]The main causes of hypoxic hepatitis include severe sepsis, cardiovascular instability, MDMA toxicity and cocaine toxicity. Cardiac failure resulting in hepatic hypoperfusion should not be forgotten and a low threshold for quantifying suspected cardiac dysfunction by echocardiography in the face of worsening liver function tests/coagulation parameters should be adopted in the critical care setting

Table 9.7 Clinical features of acute liver failure and the resultant management issues and therapy

System	Characteristics	Clinical manifestation	Management
Neurological	Hepatic encephalopathy, cerebral oedema, intracranial hypertension	Altered consciousness, progressive neurological dysfunction, risk of aspiration pneumonitis	Endotracheal intubation Neuroprotective measures Vigorous treatment of fever Treatment of hyponatraemia
Cardiac	High output state, myocardial injury	Hypotension Intravascular volume depletion Vasodilation	Correction of volume depletion Vasopressor and Inotropic support
Respiratory	Acute lung injury, Acute respiratory distress syndrome	Respiratory failure	Positive pressure ventilation lung protective strategies
Pancreas	Pancreatitis (especially in paracetamol-related disease)		Supportive care
Hepatic	Loss of metabolic function, marked decrease in: gluconeogenesis, lactate clearance, ammonia clearance, synthetic capacity	Hypoglycaemia Lactic acidosis Altered drug metabolism Neurological disturbance	Maintain normoglycaemia Intravenous acetylcysteine Review of drugs administration
Renal	Primary failure especially in acetaminophen disease, secondary failure with progressing liver and cardiac dysfunction	Hyponatraemia Impaired drug clearance Disturbed fluid and acid-base status	Fluid management Renal replacement therapy Review of drugs administration
Haematological/ Immunological	Bone marrow suppression especially in viral disease, impaired leukocyte function, decreased compliment production and cytokine clearance	High risk of sepsis Coagulopathy Thrombocytopenia Hypofibrinogenaemia	No routine correction of coagulation abnormalities Antibiotic prophylaxis
Systemic inflammatory response	High energy expenditure, increased rate of catabolism	Magnitude of SIRS correlates to progression to encephalopathy and mortality [13]	Nutritional support

Adapted from Bernal [12]

is the sedating agent of choice. Use of suxamethonium as part of a 'rapid sequence induction' is debatable in view of effects on intracranial pressure (ICP). Drugs with hepatic metabolism are avoided in favour of those with extra-hepatic metabolism (e.g. Atracurium – Hoffman degradation, Remifentanil – plasma esterase). The routine use of infusions of neuromuscular blockade is not recommended due to associations with neuromyopathy and ventilator associated pneumonia even in cases of raised ICP. Tracheal intubation and artificial ventilation for encephalopathy requires standard neuroprotection strategies to be employed to counter lability in ICP.

Respiratory care is based on the use of lung protective strategies with low tidal volumes, judicious use of PEEP and avoiding high peak airway pressures. Intrapulmonary shunts are uncommon in acute liver failure in contrast to chronic liver disease where the hepato-pulmonary syndrome can occur. Physiotherapy and respiratory toileting should be undertaken with caution due to the risk of bleeding and increasing ICP.

Cardiovascular effects of hypotension due to a low systemic vascular resistance in association with a high cardiac output are to be expected, often worsened by concurrent infections and hypovolaemia. Patients presenting with acute liver failure typically require fluid resuscitation to correct hypovolaemia and resulting hypoperfusion. It is not atypical to see a profound metabolic derangement fulfilling the King's criteria upon admission to ICU to normalise with adequate resuscitation. The choice of fluid is dependent on clinical preference, with the caveat that lactate containing fluids and 5 % dextrose should be avoided. The use of 5 % dextrose in acute liver failure risks hyponatraemia, cerebral oedema and worsening intracranial hypertension [14]. The livers' inability to efficiently clear lactate and the likelihood of a type 1 lactic acidosis precludes the use of the former.

Norepinephrine is the vasopressor of choice once intravascular volume has been restored with the aim of maintaining end organ perfusion [15]. The use of terlipressin in addition to norepinephrine has been shown to increase cerebral perfusion pressure with little effect on intracranial pressure and cerebral lactate when catecholamines alone cannot maintain adequate blood pressure [15].

In acute liver failure, high-grade encephalopathy is usually due to increasing cerebral oedema and intracranial hypertension. The incidence of intracranial hypertension is about 20–30 % in all patients with acute liver failure [16]. Table 9.8 lists risk factors associated with the development of intracranial hypertension in patients with acute liver failure.

Table 9.8 Risk factors for the development of intracranial hypertension in patients with acute liver failure

Jaundice → encephalopathy time	Hyperacute > acute > subacute
Severity of organ failure	↑ severity of organ failure + – superimposed infection = ↑ risk
Patients of age	↑ risk with younger age
Arterial ammonia	↑ risk with higher arterial ammonia concentration
Serum sodium	↓ serum sodium (130 mmol/l) = ↑ risk
Jugular venous saturation	JV saturation <55 % and >80 % = ↑ risk

As such, management strategies place importance on the recognition and subsequent monitoring and treatment of intracranial hypertension. Direct ICP monitoring is employed for real-time monitoring of ICP and can be combined with jugular bulb saturations (via a retrograde bulb catheter) to allow for closer monitoring.

Ammonia is implicated in the pathology of cerebral oedema and there is a close relationship between elevated arterial ammonia levels and the development of encephalopathy, with the risk of intracranial hypertension greatest when there is a sustained level of ammonia between 150 and 200 μmol per litre [12, 16, 17]. Furthermore, at serum ammonia levels of <75 μmol/L, intracranial hypertension rarely happens. Levels of >100 μmol/L is an independent risk factor for the development of high-grade encephalopathy, whilst levels >200 μmol/L predicts intracranial hypertension [18].

One hypothesis explaining the pathophysiology of cerebral oedema in acute liver failure is that high levels of serum ammonia induce a build-up of glutamine in astrocytes (as astrocytes contain glutamine synthetase which utilises ammonia to combine it with glutamate to produce glutamine), thus increasing osmotic potential and absorption of water. In chronic liver failure, there is time for adaptation to this increase in osmotic potential.

Cerebral blood flow varies greatly in patients with acute liver failure with the normal physiology to include 'autoregulatory' processes and the relationships between cerebral metabolism and flow being disturbed [19, 20]. As such, potential increases in cerebral blood flow in an already oedematous brain attenuate associated rises in intracranial pressure. It should be noted that there is no evidence for any disruption in the blood brain barrier. Because of this loss of 'autoregulation' the use of cerebral perfusion pressure (CPP) targets is less useful as attempts to increase CPP via mean arterial pressure (MAP) result in increases in ICP as brain volume increases. CPP is best maintained in acute liver failure by decreasing ICP and aiming for a MAP that does not result in an ICP above 25 mmHg [21].

In managing a patient with acute liver failure and possible raised ICP it is important to consider the identification of those at risk, monitoring of ICP and brain function, prophylactic therapy and overall management strategies [21].

9.4.1 ICP Monitoring

Imaging modalities like computerised tomography are able to detect cerebral oedema but are insensitive to the extent of intracranial hypertension.

There is controversy surrounding the use of direct monitoring of intracranial pressure due to the lack of evidence for improved outcomes and risk of intracranial bleeding including death.

Advocates for intracranial pressure monitoring state that medical interventions can reduce ICP and its consequences, which in turn leads to an increase in intervention rates and ICU survival [22]. However, ICP monitoring may only reduce the specific risk of cerebral death whilst the chances of death due to multi-organ failure and sepsis remain unchanged. Furthermore, an unknown ICP tends to result in indecision or occasionally overtreatment. Knowledge of ICP can be beneficial in

provision of basic aspects of general care like sedation holds and trachea-bronchial toileting more confidently.

In which patients would an intracranial bolt be suitable? The following are indications for invasive ICP monitoring [12]:

- Patients with clinical signs of a raised ICP
- Patients with concurrent multi-organ failure [17]
- Sustained ammonia levels of >200 μmol/L

Critically raised intracranial pressure can be managed with Mannitol 20 % at 2 mL/kg aiming to keep osmolality <320 mOsm/L). If the patient is oliguric, then the administration of Mannitol must be accompanied by renal replacement therapy where as a guide, two to three times the administered volume should be removed.

Hyponatraemia is associated with poor outcome in acute liver failure. The mechanism for hyponatraemia in acute liver failure is different to the secondary hyperaldosteronism causing hyponatraemia in chronic liver failure. There is an inverse relationship between intracranial pressure and serum sodium. The risk of developing intracranial hypertension is decreased by raising serum sodium to between 145 and 155 mmol/L with hypertonic saline [14]. Therefore the use hypertonic saline to increase serum sodium is an accepted strategy in maintaining ICP (Box 9.2).

Indomethacin can induce cerebral vasoconstriction and reduce ICP without impairing cerebral oxygenation and along with hypothermia, increased sedation and hyperventilation, it can be used as a method of reducing ICP.

Box 9.2. Management of Raised ICP

Sustained rise of ICP > 25 mmHg (5 min or more)

↓

Mannitol 100 ml of 20 % or 0.5 g / kg

↓

20 ml of 30 % NaCL or 200 ml of 3 % NaCL aiming to keep serum sodium at < 150 mmol / L

↓

Attempt to maintain CPP > 40 mmHg with fluids and vasopressor

Also consider:

Indomethacin 25 mg if JV sats >80 %
Hypothermia
Increase sedation with Propofol
Thiopentone bolus 125 mg
Hyperventilation (monitor Jugular bulb saturation)

Induced hypothermia results in a reduction in basal metabolism as well as reduced production, cerebral uptake and metabolism of ammonia. It also reduces cerebral blood flow [23]. In view of the systemic problems associated with hypothermia as well as the risk that it could impair hepatic regeneration alternative strategies should be adopted first before inducing hypothermia.

9.4.2 Renal Failure

The presence of renal failure in association with acute liver failure is a poor prognostic indicator, with the exception of when the underlying aetiology is paracetamol overdose. Renal failure is very common in paracetamol-induced liver failure and rarely leads to chronic renal impairment.

Continuous renal replacement therapy should be employed over intermittent haemodialysis once a decision for renal replacement therapy is made.

Regional citrate anticoagulation is increasingly employed in the care of critically ill patients with liver failure and in those undergoing liver transplantation due to the high risk of haemorrhage. Although rare, heparin-induced thrombocytopenia (HIT) in acute liver failure patients including those undergoing liver transplantation is potentially catastrophic for a new graft. A recent review cited the incidence to be about 2 % in patients undergoing transplantation [24]. As we know, the duration of heparin therapy is a significant risk factor in the development of HIT [25]; thus, it is understandable that heparin sparing methods of anticoagulation like regional citrate anticoagulation is desirable in patients who may require renal replacement therapy, before, during and after transplantation.

It should also be noted that in the absence of renal failure, renal replacement therapy can also be used in patients to control hyperammonaemia and temperature control in situations of raised intracranial pressure [21].

9.4.3 Immunity

A failing liver results in compromise of adaptive and innate immunity. Impaired compliment synthesis combined with macrophage (Kupffer cell), natural killer and natural killer T cell dysfunction result in an increased susceptibility to bacterial and fungal infections, reduced recruitment of circulating lymphocytes and impaired modulation of liver injury [26]. Sepsis is a major cause of mortality, and it should be noted that the usual signs of sepsis (pyrexia and leucocytosis) may not always be present. Infections early in the illness are typically gram positive commonly caused by *Staphylococcus aureus*, whilst gram negative infections caused by *Escherichia coli* are seen later. Fungal infections are nearly invariably caused by *Candida albicans* and are seen in about a third of cases.

Prophylactic antibiotics covering both gram positive and gram negative organisms (e.g. piperacillin with tazobactam) and antifungal (e.g. fluconazole) should be administered at admission and certainly with the advent of a deteriorating synthetic function.

9.4.4 Nutrition

Patients with acute liver failure have high energy expenditure and protein catabolism and thus have a requirement for nutritional support to avoid a negative impact on immune function. There is a paucity of data in relation to nutrition in acute liver failure and guidance here is given according to best practice.

Hypoglycaemia is seen due to loss of hepatic glycogen stores and impaired gluconeogenesis. Intravenous glucose replacement is required especially prior to the establishment of enteral feeding or if malabsorption is present [3]. Tight glycaemic control is no longer warranted but hyperglycaemia should be avoided due to its association with intracranial hypertension and poor ICP control in acute liver failure [27].

Most European liver centres favour enteral feeding via a nasoduodenal tube if possible [28]. The siting of a nasoduodenal tube should not delay the initiation of enteral feeding via a nasogastric tube if this is better facilitated. Furthermore, if enteral nutrition is poorly tolerated then parenteral nutrition should be commenced.

The recommended amount of enteral feed is based on general dosage in critical care. Glucose, lactate, triglycerides, phosphates and ammonia levels should be closely monitored [29]. Hypophosphataemia is a common sequelae in acute liver failure but also when renal replacement therapy is employed. However, it can also be indicative of increased ATP (adenosine triphosphate) utilisation when the previously failing liver undergoes regeneration [30].

Feeding should be commenced within 24 h of ICU admission aiming for 25–30 kcal per kg per day. Usually 1.0–1.5 g of enteral protein per kilogramme per day can be administered without worsening hyperammonaemia or hepatic encephalopathy. However, it is advisable to measure blood ammonia levels and lower the protein load in patients with worsening hyperammonaemia or those at risk of intracranial hypertension. The use of immunonutrition containing glutamine is contra-indicated in view of the role of glutamine in the development of cerebral oedema in acute liver failure [3, 12, 31].

9.5 Aetiology Specific Management

When appropriate, management is complimented with aetiology specific measures which are discussed below.

9.5.1 Paracetamol

Paracetamol causes toxicity in a dose dependent manner. In patients with severe paracetamol poisoning, it is accepted that the interval between drug ingestion and treatment with acetylcysteine is closely related to outcome [32].

Ingestion of doses of more than 150 mg/kg can cause toxicity but it should be noted that toxicity has been observed when doses of between 3 and 4 g per day have been taken, especially in the context of high risk groups [33]. A severe drug induced

transaminitis, typically in the thousands iu/l, is seen. Its commonality, especially in the western world means that paracetamol levels should be requested in all patients presenting with acute liver failure or hepatitis [2]. It cannot be overstated that paracetamol levels must be interpreted in conjunction with a thorough history and that cases of delayed presentation since time of ingestion, unintentional overdoses and staggered ingestion are usual causes of misinterpretation.

N-acetylcysteine (NAC) is a safe and effective antidote to paracetamol poisoning and its administration is mandatory in proven and suspected cases, even up to 48 h post ingestion [34]. For cases, presenting within a few hours of ingestion, the administration of activated charcoal is most effective within 1 h [35] of ingestion but can be of benefit as long as 4 h after ingestion [36]. Furthermore, the administration of activated charcoal does not interact or reduce the effect of *N*-acetylcysteine [36]. In the UK, *N*-acetylcysteine is administered via the intravenous route as follows: loading dose of 150 mg/kg in 5 % Dextrose over 60 min (previously 15 min) and a maintenance dose of 50 mg/kg over 4 h followed by 100 mg/kg over 16 h. Some UK liver units use variations of this regimen, and early consultation with the regional liver unit is advised especially in high risk cases.

The administration of *N*-acetylcysteine in conjunction with its standard toxicity nomogram [37] is advised. New simplified treatment guidelines including an updated treatment nomogram have now been adopted, which eliminate the old 'high risk' and 'normal risk' treatment line (Fig. 9.1) The MHRA guidance now stipulates that all patients with a timed plasma paracetamol level on or above a single treatment line joining points of 100 mg/L at 4 h and 15 mg/L at 15 h after ingestion, should receive *N*-acetylcysteine. Despite this, caution needs to be exercised in cases of multiple doses ingested over time and in high risk groups (e.g. patients on enzyme inducing drugs, chronic alcohol abuse, patients with malnutrition or anorexia nervosa) [38] where the new guidelines suggest that if there is doubt over the timing of ingestion or in staggered overdose, the nomogram should not be used and *N*-acetylcysteine given immediately. The initial dose should now be given over 60 min to reduce the risk of dose-related adverse reactions. Furthermore, hypersensitivity is no longer a contra-indication to treatment with *N*-acetylcysteine [11].

When to stop *N*-acetylcysteine therapy? This remains a controversial area and no definitive statement can be made, other than to suggest safe practice would dictate in conjunction with the patients' clinical condition, liver biochemistry, ingestion history and regional liver unit advice if applicable. If in doubt, do seek advice.

9.5.2 Mushroom Poisoning

Amanita phalloides, also known as the death cap mushroom is a highly toxic fungus, responsible for the majority of fatal mushroom poisonings worldwide, usually due to errors in identification because of similarities in appearance to edible varieties.

There is no definitive investigation to confirm poisoning by Amanita phalloides, but questioning during the history regarding mushroom ingestion, especially if gastrointestinal symptoms are present, will usually result in the diagnosis being made.

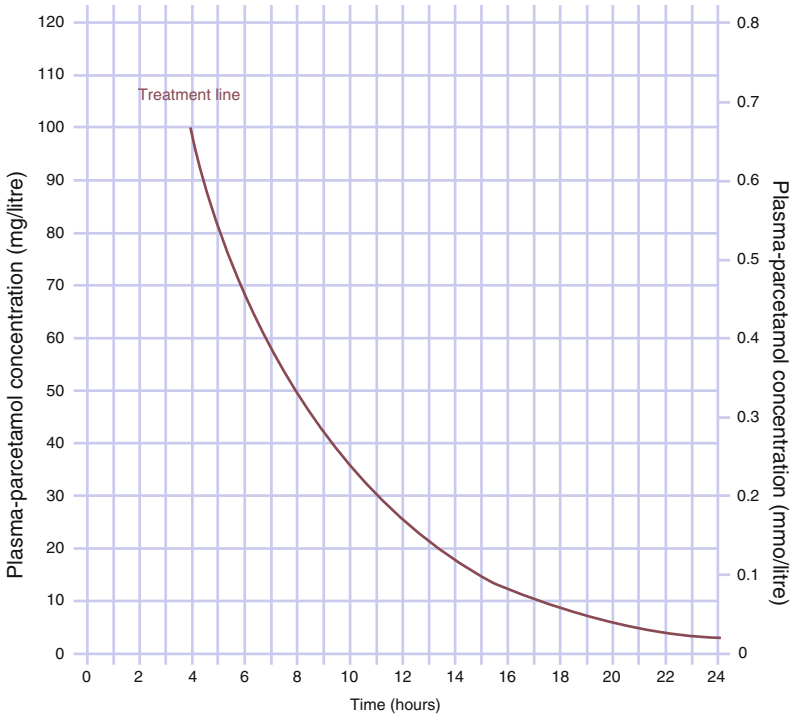

Fig. 9.1 Treatment nomogram for paracetamol overdose courtesy of the MHRA (UK). This material is printed with the permission of the Medicines and Healthcare products Regulatory Agency under delegated authority from the Controller of HMSO. Should you wish to reuse this material please contact this agency

Historically, survival rates have been poor without liver transplantation, but complete recovery has been described with supportive care and medical treatment with either Penicillin G or Silibinin [39]. Silibinin (30–40 mg/kg/day intravenously) is thought to be more successful than Penicillin G but its use may be limited by local availability. Administration of *N*-acetylcysteine is also recommended. Early discussion with the regional liver unit is advised as patients with acute liver failure due to mushroom poisoning are expeditiously transferred and cared for in regional centres with an emphasis on early listing for liver transplantation as the only life saving option [8].

9.5.3 Viral Hepatitis

Hepatitis A and B, hepatitis D in a hepatitis B positive individual and hepatitis E are relatively infrequent causes of acute liver failure. It is debatable if hepatitis C can cause acute liver failure. It should be noted that reactivation of chronic hepatitis B can also occur in the setting of chemotherapy or systemic immunosuppression and

as such hepBsAg positive patients beginning such treatment are treated prohylactically with nucleoside analogues.

Herpes simplex and Varicella zoster virus are rare causes of acute liver failure but cases have been described even in previously healthy individuals [40, 41].

Acute liver failure due to Hepatitis A and E is treated with supportive care only as there is no virus-specific treatment. With respect to hepatitis B, nucleoside analogues are administered for acute treatment but also for prevention of post-transplant recurrence. Patients with herpes simplex or varicella zoster as the cause of acute liver failure should be treated with acyclovir and are not to be excluded from transplantation [8].

9.5.4 Wilson's Disease

Whilst a chronic disease, it can present as an acute decompensation which is accepted as a causative presentation of acute liver failure, because when this occurs it is usually fatal without transplantation. It usually presents with a sudden onset Coombs negative haemolytic anaemia and jaundice, typically in a young patient.

Interestingly, Kayser-Fleischer rings are seen in about 50 % of patients presenting with acute liver failure due to Wilson's disease [42]. As such, any suspected case warrants an Ophthalmology assessment, even on the intensive care unit as this can expedite specialist referral and consideration for transplantation, especially whilst other biochemistry results are pending.

Another rapid and reliable alternative to serum caeruloplasmin and urinary and serum copper analysis, is a high bilirubin (mg/dl) to alkaline phosphatase (iu/l) ratio. Typically a figure of >2.0 is accepted as a reliable indirect indicator of Wilson's disease [42, 43].

Renal impairment is common due to copper deposition in renal tubules, which could result in renal tubular acidosis and even Fanconi's syndrome. Renal replacement therapy is typically required not only for kidney support but also for the fact that it acutely lowers serum copper and limits further haemolysis [8].

The use of penicillamine for the treatment of Wilson's disease in the context of acute liver failure is not recommended in contrast to chronic disease [8].

9.5.5 Autoimmune Hepatitis

Similar to Wilson's disease, this chronic condition can present as an acute decompensation of undiagnosed liver disease, which can be considered as acute liver failure.

Whilst the use of steroids in acute liver failure per se is not recommended, in the context of autoimmune hepatitis presenting as acute liver failure, which is representative of a severe form of the disease, a trial of high dose steroids in conjunction with specialist advice can be considered. However, as the severity of the disease is such that some cases would require transplantation, referral and transfer to a specialist liver unit should not be delayed pending a response to steroid treatment [8].

9.5.6 Acute Fatty Liver of Pregnancy/HELLP (Haemolysis, Elevated Liver Enzymes, Low Platelets) Syndrome

A rare disease of pregnancy, which develops as women near term (typically last trimester), it is associated with foetal and maternal mortality.

The triad of jaundice, coagulopathy and thrombocytopenia is seen with hypoglycaemia and features of pre-eclampsia like hypertension and proteinuria. Steatosis may be seen on imaging (ultrasound scan or computed tomography).

The over-riding priority once the syndrome has been recognised is prompt delivery of the foetus and post delivery supportive care for optimal maternal and foetal outcome [8].

Whilst full recovery post delivery is usual, occasionally deterioration does occur.

9.5.7 Acute Ischaemic Liver

Usually seen after cardiac arrest, it can also occur in any situation resulting in significant hypotension or hepatic hypoperfusion. Presentation can be anything on a spectrum from a self-limiting transaminitis to established acute liver failure. It should be noted that drug-induced hypoperfusion has been described due to recreational drugs like cocaine [44] and methamphetamines [45].

A shocked liver in isolation is rare and usually concurrent renal failure occurs especially if the underlying aetiology is due to cardiac dysfunction. In cases of drug-induced hepatic dysfunction, rhabdomyolysis can also cause renal dysfunction.

Management is typically cardiovascular support and transplantation is seldom warranted or feasible.

9.5.8 Budd-Chiari Syndrome

Acute hepatic vein thrombosis can present as acute liver failure. Typically in the presence of ascites and hepatic enlargement, the diagnosis is made via suitable imaging studies (ultrasound scan, computed tomography, venography or magnetic resonance venography).

Venous decompression is attempted but if unsuccessful and in the presence of acute liver failure transplantation may be the only option, provided underlying malignancy is excluded.

If Budd-Chiari is confirmed on imaging then further investigations are needed for potential underlying causes, to include but not limited to tumour markers, protein C, protein S, Factor V Leiden and Antithrombin III.

9.5.9 Acute-on-Chronic Liver Failure

As stated earlier, acute liver failure is thankfully rare. The intensive care clinician is more likely to encounter a ‘decompensation’ of chronic liver disease, also

Table 9.9 Precipitating causes of acute-on-chronic liver failure and specific treatment

Alcoholic hepatitis	Nutritional support If Maddrey's [46] score >32 consider steroids
Varices/portal hypertension	Antimicrobial therapy, endoscopic banding, somatostatin analogues (e.g. terlipressin), Sengstaken–Blakemore tube, TIPSS (transjugular porto-systemic shunt)
Spontaneous bacterial peritonitis	Antimicrobials if ascitic neutrophil count >250/mm^3 or cell positive sample, intravenous albumin to prevent hepato-renal syndrome, prokinetics
Systemic inflammation (e.g. sepsis, surgery)	Antimicrobial therapy

known as acute-on-chronic liver failure. It is imperative that the intensive care clinician can recognise an acute decompensation of a cirrhotic patient as a separate entity from acute liver failure most notably because of differences in management and prognosis including the likely benefit or otherwise of supportive therapy on the ICU.

The patient with deteriorating 'end stage' liver disease should be appropriately identified. Such differentiations are at the behest of a good history, eliciting precipitating factors or causative aetiologies and a careful assessment of recent biochemistry and imaging. The patient with 'end stage' liver disease exhibits a gradual decline in clinical status and liver function without a precipitating cause. Organ support in such setting is usually futile.

Acute-on-chronic liver failure is identified when the pattern of symptoms and signs associated with acute liver failure are present on a background of chronic disease (cirrhosis) which has progressed to demonstrate stigmata of portal hypertension like ascites and variceal bleeding.

Patients with compensated cirrhosis usually decompensate due to a 'systemic' stress, usually sepsis or gastrointestinal haemorrhage, or due to a direct insult to the liver, like ischaemia or toxins like alcohol or drugs. Importantly, if these precipitating events are identified and appropriately treated then reversibility in the deterioration in liver function can be expected. Therefore, identifying such patients can be reassuring in the provision of continuing organ support (Table 9.9).

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The Initial Surgical Management of the Critically Ill Burn Patient

10

Jorge Leon-Villapalos

Summary of Abbreviations

ATLS	Advanced Trauma Life Support
EMSB	Emergency Management of Severe Burns
SSSS	Staphylococcal scalded skin syndrome
TBSA	Total body surface area
TENS	Toxic epidermal necrolysis syndrome
TSS	Toxic shock syndrome

10.1 Introduction

Burns are disruptions of tissue architecture that are commonly caused by thermal injury and also by a number of other aetiologies including electricity, chemical agents and radiation.

There are other conditions that can mimic local burn tissue injury in physiopathology: wound behaviour and surgical management without being burns themselves. These include cold-induced injuries and exfoliative disorders of the dermo-epidermal junction such as toxic epidermal necrolysis syndrome (TENS) and staphylococcal scalded skin syndrome (SSSS).

Burns are still frequent events that require specialised units harbouring a multidisciplinary team with resources, expertise and knowledge not only in the initial and acute management of the burn injury, but also in the process of recovery and rehabilitation.

From the epidemiological point of view, approximately 250,000 people suffer injuries related to burns in the UK, 175,000 require assessment in the Accident and

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_10

Emergency Department and 13,000 need to be admitted for specialised treatment to the burns unit.

Despite improvements in survival, there are 300 fatalities a year from burn injuries in the UK, mainly in the over 60-year-old group, the only group in which mortality for burn injury remains relatively unchanged [1]. Recent reviews suggest a connection between socio-economic status and age in the severity of burn injury [2, 3].

Even though small burns can have a deep impact in patients from both the physical and emotional point of view, the scope of this chapter is directed towards the surgical management of the major burn.

A major burn can be defined in a variety of ways. From the logistic and resource point of view, a major burn can be considered as those when the patient requires hospital admission, operative management and fluid resuscitation.

From the physiological point of view, major burns can be defined as those that elicit a major hypermetabolic response that differs from other types of trauma and critical illness in its severity and duration.

Characteristically, this occurs when burns involve more than 20 % of the total body surface area (TBSA). In this situation the metabolic rate can be increased by nearly 50 %, and even further in larger burns or when sepsis is present [4].

Even though hypermetabolism follows any form of trauma or critical illness, burn injuries differ from these in the severity and duration of this response that can last up to a year post burn [5].

This chapter will then aim to describe the Initial surgical management of the burn-injured patient and the need for interaction with other professionals of the multidisciplinary team, specifically the intensive care team.

The ultimate role of the surgeon in the management of the burn wound is the early debridement and soft tissue cover of the wound, but prior to this, there is a need to describe the importance of preoperative optimisation.

Optimisation includes adequate assessment and resuscitation, control of hypermetabolic response in terms of temperature, blood loss, nutrition, infection and pharmacological modulation.

10.2 Understanding Burns Management Principles

Reduction in mortality and in-patient hospital stay is based in a better understanding of burns management principles by an expert and cohesive multidisciplinary burns team.

The multidisciplinary team manages the patient not only from the acute point of view, but also from the therapy and rehabilitation of both physical and emotional aspects.

All members of the multidisciplinary team, of which surgery and intensive care are part, combine their use of resources and expertise to restore anatomy, cosmetic appearance and function and to facilitate the return of the burn victim to society as a fully active individual.

The following principles need to be taken into consideration:

10.2.1 Pre-hospital and Early Management

10.2.1.1 First Aid

Pre-hospital management includes the prompt application of first aid aimed at stopping the burn process, cooling the burn wound, whilst keeping the patient warm and covering the burned area.

Stopping the burning process involves the safe removal of the victim from the source of the burn and extinguishing the burning clothing using water or the 'drop and roll' method.

Cooling the burn wound with running tap cool water for at least 20 min decreases the progression to a deeper pattern of the burn wound [6, 7] and is beneficial for up to 3 h post injury. Other beneficial effects of water-cooling include pain relief, decrease cell damage, reduction of oedema and decreased inflammatory response [8].

All burning clothing and jewellery must be removed and the wound needs to be covered with loosely applied cling film or another atraumatic dressing that allows easy inspection of the wound.

Cooling the burn wound needs to be balanced with keeping the patient warm, which is especially important in the paediatric patient. This is of paramount importance to avoid the onset of hypothermia and acidosis, both of which have a noxious effect on the operative management of the patient, delaying the debridement of the wound and increase the potential for blood loss.

The British Burns Association resumes the need for first aid in the following recommendations: 'Cool, Call and Cover [9]':

1. Cool the burn with running cold tap water for 20 min and remove all clothing and jewellery.
2. Call for help – 999, 111 or local GP for advice.
3. Cover with cling film or a sterile, non-fluffy dressing or cloth. Make sure the patient is kept warm.

10.2.2 Initial Assessment

Following first aid, early management includes the assessment of the patient according to recognised protocols of trauma management (Fig. 10.1).

Frameworks of trauma such as Advancement Trauma Life Support (ATLS) or Emergency Management of Severe Burns (EMSB) provide the burns professional with treatment priority principles that emphasise the fact that timely resuscitation, assessment and recognition of life threatening injuries, together with early transfer to a definitive burns unit saves lives.

Fig. 10.1 Early management algorithm

The recognised classic treatment algorithm of primary survey with the ABCDE (Airway, Breathing, Circulation, Disability and Environment/Hypothermia protection) approach, tip-to-toe secondary survey and continuous reassessment with definitive transfer to and expert facility displays a number of variations in the management of burn patients.

The potential for an impending airway compromise in major burns with an inhalational injury will require the early involvement of the Anaesthesia/Intensive Care teams in order to secure a definitive airway in the form of an endotracheal tube. Airway assessment and the possibility of an inhalational injury, especially if the injury has occurred in an enclosed space, need to be coupled with the careful assessment for potential injury of the cervical spine.

Potential inability or delay in weaning off burns patients from mechanical ventilation may require the insertion of a tracheostomy either through a percutaneous or open surgical method. Both methods are safe in expert hands with the choice of method depending on the state of the soft tissues of the neck affected by the burn,

experience of the operator and the size of the burn and the body habitus of the patient. Tracheostomy is therefore a fundamental skill for both the burn surgeon and the intensive care specialist [10].

The adequacy of the oxygenation and ventilation may be compromised by the presence of full thickness burns of the chest wall and abdomen leading to decreased compliance and high inflation pressures (Fig. 10.2).

The full thickness skin eschar acts as a ventilation compliance-limiting factor. The presence of ventilation difficulties should prompt urgent assessment of the need for releasing escharotomy incisions performed under suitable theatre conditions and by professionals with adequate experience. Escharotomies will immediately improve ventilation and avert the possibility of abdominal compartment pressure [11, 12].

Escharotomies in the chest and abdomen are performed from unburned skin to unburned skin and along the anterior axillary lines and across the lower edge of the rib cage transversely. Occasionally there is a need to join these lines to provide a more definitive release that is ensured by direct visualisation of healthy bulging fat through the escharotomy incisions [13].

The adequacy of the circulation in the burns patient requires prompt insertion of Intravenous access in the form of two large cannulas preferably through unburned

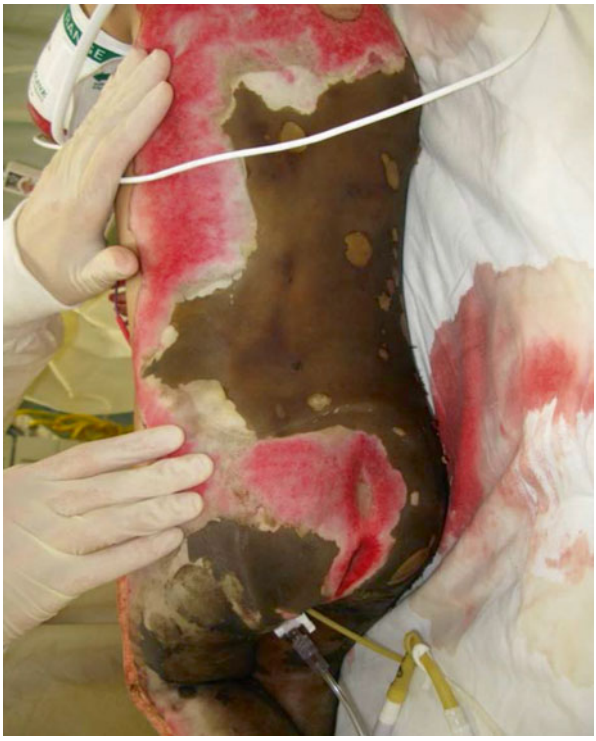

Fig. 10.2 Full thickness burn to the chest wall

skin in order to promptly avert the hypovolemia that occurs as a consequence of the burns distributive shock.

In the case of full thickness circumferential burns to the limbs, the need for escharotomies in order to ensure adequate distal blood flow to the extremities is an urgent priority [14].

Upper limb escharotomies (Fig. 10.3) are performed along the lateral and medial axial lines with the arm in pronation applying the principles described above. Great care must be exerted to avoid damage to relevant neurovascular structures, especially around the medial epicondyle area, where the ulnar nerve is at great risk. When electrical injury is the cause of the soft tissue damage, the presence of muscle necrosis due to compartment syndrome may require the combination of escharotomies with fasciotomies in order to provide limb salvage and function preservation.

Lower limb escharotomies are performed also along lateral and medial axial lines down to healthy bulging fat avoiding damage to the common peroneal nerve at the level of the fibular neck laterally and proximally, and to the posterior tibial neurovascular bundle and the great saphenous vein distally.

Disability and neurological assessment of the critically ill major burned patient can be problematic and difficult to ascertain due to the fact that the patient may have

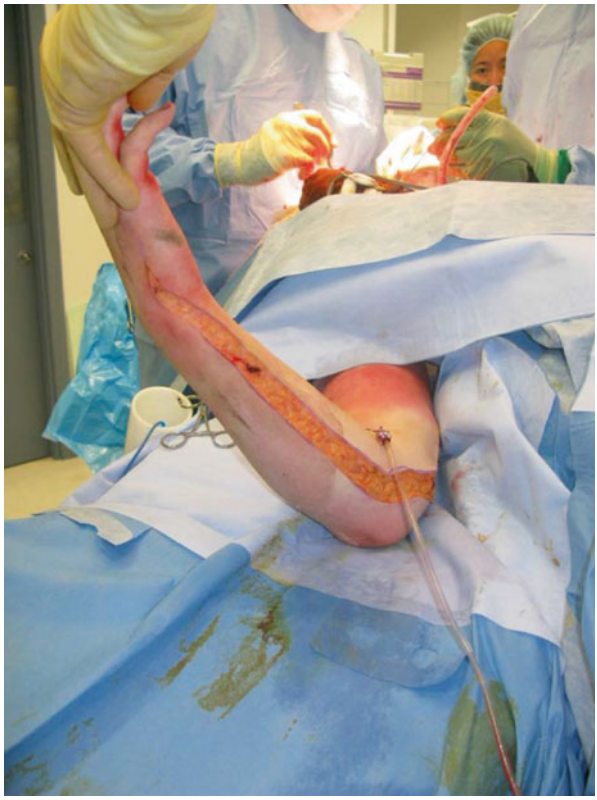

Fig. 10.3 Upper limb escharotomy

been intubated onsite, In this case, obtaining a good burns and trauma history and performing a thorough physical examination will help to develop a high degree of suspicion and to exclude the possibility of a brain or spinal injury. Any lack of normalisation of neurological function following decrease of sedation and analgesia or a failed extubation should alert the burns professional about the possibility of neurological damage.

From the environmental point of view, hypothermia is often an overlooked risk factor in the management of the major burn, the importance of which cannot be overstated. Continuous reassessment is fundamental whilst resuscitating the patient in order to prevent the early onset of the lethal triad of hypothermia, acidosis and coagulopathy in burns, which is associated with significant mortality [15].

The importance of these complications cannot be underestimated taking into consideration the established practice of early excision of the burn wound that may involve severe blood loss potentially increased by a deranged clotting cascade and lack of platelet adhesion accentuated by hypothermia.

Keeping the patient warm at pre-hospital level and during transfer can therefore avert the delay in acute surgical debridement due to hypothermia. Temperature control can be achieved by the use of radiant heaters in the Emergency Department, and by keeping these patients in a warm room whilst in the burns unit. The infusion of warm intravenous fluids via new generation intravascular warming catheters and forced hot air technologies, such as such as the Bair Hugger™, are methods commonly used to avoid hypothermia [16].

Hypothermia can decrease the ability of the burn patient to withstand the stress of surgery and become less tolerant to the effect of anaesthetic drugs [17].

Adequate assessment of the burn wound in size and depth are performed in order to provide priorities of treatment.

Burns surgery is ultimately aimed at preserving the blood supply of the skin and all of the skin functions which include protection from environmental elements and pathological organisms, immunological surveillance, fluid and electrolyte homeostasis, maintenance of protein and electrolyte concentrations, thermoregulation and control of heat loss.

10.2.3 Assessment of the Burn Wound

The assessment of the size of the burn wound can be performed by clinical methods or chart-based methods, but in the acute situation it is frequent to use a combination of both depending on the resources available and the experience of the clinician.

The Wallace rule of nines [18], serial halving [19], modified Lund and Browder charts [20, 21] and the use of the palm of the patient's hand as a percentage calculator [22] are recognised methods for calculation of the burned total body surface area. These methods provide an estimation of the total body surface area, but the burn injury can be over calculated in the case of small burns and under assessed in larger injuries. These inaccuracies can have a direct effect on the resuscitation regime applied and can result in serious under or over resuscitation [23].

Clinical experience provides a theoretical advantage in the assessment of total body surface area, but it is not infallible. A recent review proved the difficulties of burn area accuracy assessment in trauma situations by experienced teams not only in civil situations but also in military environment [24].

Modern technologies are likely to overcome the relative subjectivity of some of these assessment methods. The increased accuracy of software and mobile technology has already started to produce interesting diagnostic tools that supplement clinical judgement [25, 26].

In terms of depth, burn injuries are classified according to the damage to the epidermal and dermal layers of the skin layers of the skin.

Burns are dynamic injuries characterised by three distinct areas of thermal damage: a central area of non-salvageable necrosis, a potentially salvageable area of stasis characterised by the outpouring of inflammatory mediators and by its responsiveness to early resuscitation and early debridement and an area of surrounding inflammation and vasodilatation [27].

The clinical parameters that define the classification of burn injuries in terms of depth are the colour, capillary refill, sensation, presence of blisters and potential for self-healing.

Burns can then be classified into superficial or epidermal burns, dermal or partial thickness burns and full thickness burns (Figs. 10.4, 10.5, 10.6 and 10.7).

Partial thickness burns can then be subdivided into superficial partial thickness or superficial dermal, mid-dermal partial thickness burns and deep dermal partial thickness.

This classification illustrates the progressive damage to epidermis, papillary dermis, reticular dermis and ultimately the full thickness of the skin down to the subcutaneous tissue.

It is easy to understand that as the intensity of the thermal injury increases, the damage in terms of depth will also increase.

The colour will change from a vivid pale pink with brisk capillary refill in superficial injuries to a cherry red colour in deep dermal injuries and a leathery brown-yellow presentation in full thickness wounds.

The presence of blisters represents the pathognomonic physical sign of the partial thickness burn and the actual potential skin loss that needs to be accounted into any burns area assessment. Blisters will become larger and coalesce as the burn deepens. Wounds will have a moist appearance in superficial injuries and a dry appearance in deep damage.

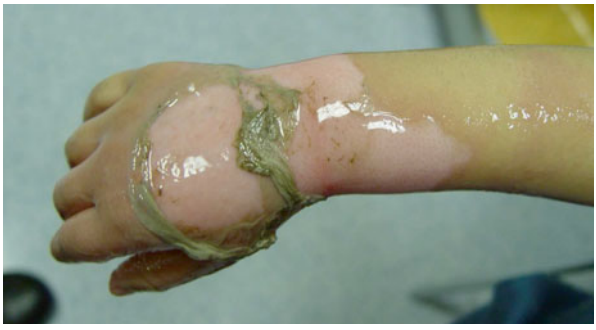

Fig. 10.4 Superficial partial thickness burns

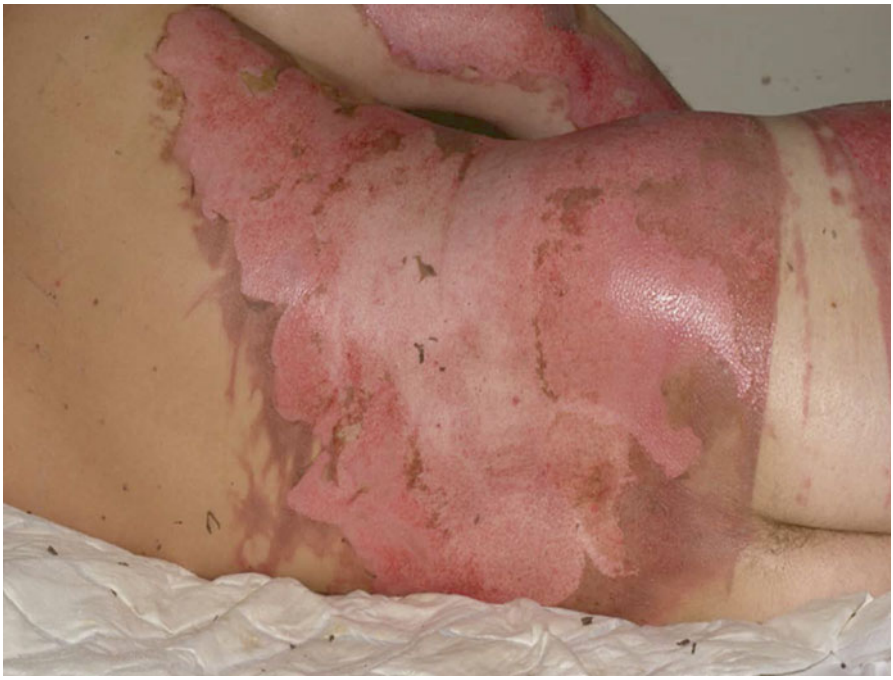

Fig. 10.5 Mid-dermal partial thickness burn

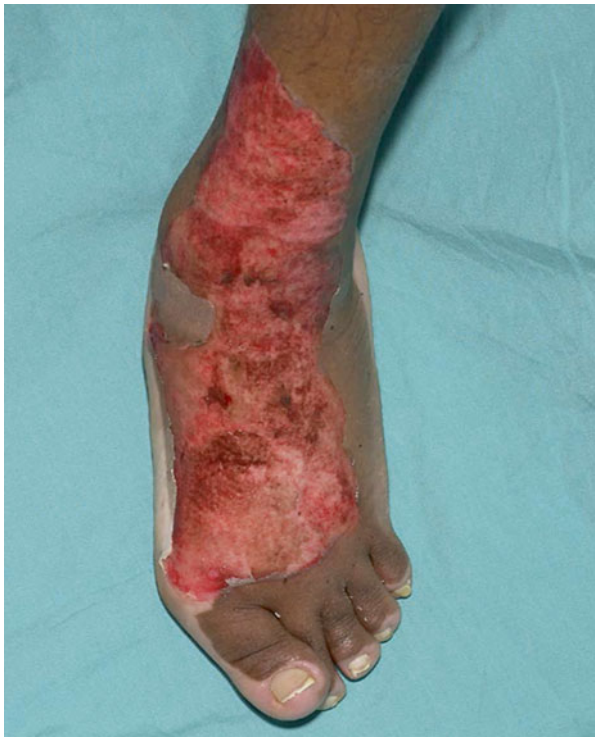

Fig. 10.6 Deep dermal partial thickness burn

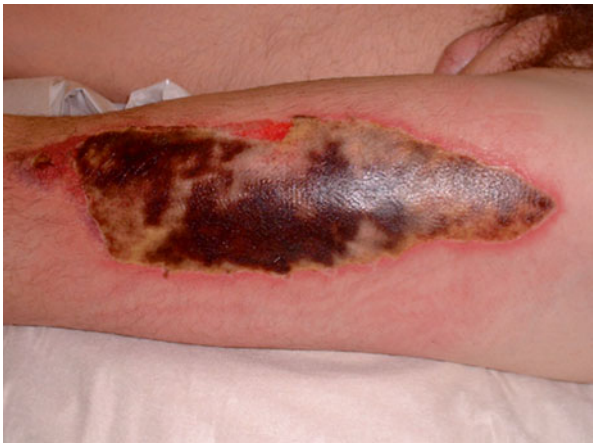

Fig. 10.7 Full thickness burn

As the blood supply decreases when the wound deepens, the damage to the sensory supply of the skin will also increase. A superficial wound will be intensely painful compared to the insensate presentation of a deep injury.

The clinical translation of a superficial injury compared with one of a deeper pattern relates to the potential need for surgical management.

A superficial partial thickness injury may require resuscitation if it is extensive, but it is likely to heal without any excisional surgery over a period of 3 weeks without developing abnormal scarring.

Any burn injury unlikely to follow a spontaneous resolution pattern within a 3-week period is likely to require surgery in order to avoid delayed healing with associated unwanted sequelae [28].

Current advances in the assessment of the depth of the burn include the use of modern imaging technologies such as Laser Doppler flowmetry.

This technique is most useful in aiding to support the burns clinician in his decision to operate or not in indeterminate- or mixed-depth burns, especially in children.

Laser Doppler imaging (LDI) is a noninvasive technique for predicting burn wound outcome based on measurement of cutaneous blood flow, measured in perfusion units (PU) and assessed by the power spectrum of Doppler frequency shift on reflected laser light [29].

Laser Doppler readings in deep burns correlate well with the need for grafting and the development at a later stage of abnormal scarring [29, 30].

10.2.4 Fluid Resuscitation

Accurate total body surface area assessment is fundamental to decide on a judicious regime of fluid resuscitation.

The Parkland formula [31] provides a common language of fluid resuscitation between burns professionals and adequate resuscitation from burn shock.

The formula: 4 ml of *Hartmann's solution* × *body weight (kg)* × *% total body surface area* provides a 24 h fluid calculation that it is administered in two distinct periods and amounts, the first half within the first 8 h of the burn injury and the second half is administered for 16 h following the first period. This split regime of resuscitation aims to overcome the phenomenon of *third spacing* and *fluid creep* that occurs during the first 24 h of fluid resuscitation and the early onset of burn oedema.

There are some variations in fluid resuscitation affecting paediatric patients. In these cases, and in addition to the resuscitation with Crystalloid, 5 % Dextrose in 0.45 % Normal Saline is given as maintenance in order to address the hypoglycaemia caused by quick depletion of glycogen deposits in children. This is administered according to body weight, with 100 cc/kg given for the first 10 kg of weight, 50 cc/kg for the next 10 kg and 20 cc/kg for any kg between 20 and 30 kg of weight.

The distributive and hypovolemic components of burn shock, that are characterised by intravascular volume depletion, low pulmonary artery occlusion pressures, elevated systemic vascular resistance and depressed cardiac output [32, 33], are averted by the early administration of intravenous fluids that constitute the most important single intervention in the care of the burn patient [34].

Monitoring of resuscitation is essential to warrant organ perfusion and positive outcomes.

Urine output of at least 0.5 cc/kg/h in adults and 1 cc/kg/h in children and resolution of any potential acidosis and/or raised markers of hypo perfusion are commonly used targets.

Factors that influence resuscitation include burn depth, Inhalational injury, associated injuries, age, delayed resuscitation, need for escharotomies, and associated alcohol and drugs intake.

Under resuscitation can lead to renal failure and inadequate tissue perfusion. Fluid overload can also lead to severe complications including compartment syndrome, intraocular hypertension, pulmonary overload and massive oedema [35].

10.2.5 Referral to a Burns Unit

Following application of the principles outlined above, to assess and resuscitate burn injuries the patient needs, once stabilised, to be safely transferred to an area of expertise for the ultimate management of the burn wounds.

The British Burns Association suggests the following minimum threshold for referral into specialised burn care services [36]:

- All burns ≥2 % TBSA in children or ≥3 % in adults.
- All full thickness burns.
- All circumferential burns.
- Any burn not healed in 2 weeks.

- Any burn with suspicion of non-accidental injury should be referred to a Burn Unit/Centre for expert assessment within 24 h.

- In addition, the following aetiologies should prompt a discussion with a Burns Consultant for consideration of referral:
  - All burns to hands, feet, face, perineum or genitalia.
  - Any chemical, electrical or friction burn.
  - Any cold injury.
  - Any unwell/febrile child with a burn.
  - Any concerns regarding burn injuries and co-morbidities that may affect treatment or healing of the burn.
  - If the above criteria/threshold is not met then continue with local care and dressings as required.
  - If burn wound changes in appearance/signs of infection or there are concerns regarding healing, then discuss with a specialised burn service.
  - If there is any suspicion of toxic shock syndrome (TSS) then refer early.

10.3 Surgical Management: The Burns Unit

Once stabilisation and safe transfer to the Burns unit has been achieved, a multidisciplinary team led by the burns surgeons and burn intensive care specialists continues the management of the major burn.

These are key figures whose role is complemented by a myriad of professionals within an expert multidisciplinary team composed of nurses, physiotherapists, occupational therapists, dieticians, social workers, pharmacists, play specialists and support workers.

As previously discussed, decreased mortality from major thermal Injury has been due not only to the advances in resuscitation performed in the early stages of patient management, but also to specific control of Infection, support of the hypermetabolic response to trauma and early burn wound closure. These are best treated in the environment of the burns unit.

10.3.1 Preparation for Surgery, Wound Debridement and Closure

Once it has been established that the burn injuries are of such depth that it is unlikely that they will heal by themselves (deep dermal and full thickness burns), preparations must be made for debridement of the wound and closure of burn defect to be completed as soon as possible.

The role of the burn surgeon is to provide airway management (tracheostomy), assist with ventilation (chest escharotomies), recognise and treat smoke inhalation, perform prompt circulatory optimisation with escharotomies in limbs affected with deep circumferential full thickness burns, excise the burn eschar promptly and cover

the wound with the patient's own skin (autograft) or with donor skin (allograft) or artificial substitutes (Integra®, Matriderm®, Biobrane®).

Early excision and closure of the wound provides a dramatic reduction in metabolic rate compared to a burn of the same size not excised, reduces operative blood loss, length of stay, decreases the number of septic episodes and decreases mortality in children and young adults compared to comparable size burns undergoing serial excisions [37].

The preparation for theatre includes the physiological optimisation of the patient to withstand long surgeries with the potential for massive tissue loss, the pre-warming of the operating theatre at 25–30 °C of temperature in order to avoid hypothermia, acidosis and increased blood loss, a dynamic, well prepared and enthusiastic team, the judicious ordering of blood products for potential transfusion and a constant communication between the anaesthetic and the surgical teams.

Blood loss during surgery can be dramatic and overwhelming, often requiring an exchange transfusion of more than twice the blood volume. The time since the injury influences the surgical plan, as a delayed excision and the subsequent presence of infection increases the blood loss potential.

Hemostatic measures during the surgery include the use of tumescent infiltration with Normal Saline and Adrenaline, the use of tourniquets, electrocautery, fibrin sealants and systemic haemostatic agents [38].

The ordering of blood products needs to be consistent with the amount of debridement to perform. Characteristically, there is a loss of 100–250 ml of blood (or 2–5 % of the circulating blood volume) for every 1 % TBSA that is excised and grafted [39–41].

Replacement with alternate packed red blood cells and fresh frozen plasma is usual practice.

The combined surgical/anaesthetic/intensive care team will look for parameters of stabilisation during surgery that will include

- Mean Arterial pressure: >70 mmHg
- Central Venous Pressure: ~10 mmHg
- Cardiac Output: 4–8 l/min
- Haemoglobin: 8–10 g/dl
- Ph.: Normal
- BE: <–5
- Lactate: <2 mmol/l

The role of hypothermia control during lengthy debridement surgery cannot be underestimated. Hypothermia in the perioperative period impacts greatly in the outcome of surgery and is associated with increased wound infection, altered drug metabolism, additional bleeding and need for transfusions, adverse cardiac events and increased length of stay [42].

Hypothermia increases acidosis, deranges the clotting cascade and decreases platelet adhesion. Current strategies to avert hypothermia include, in addition to the temperature control in theatre operation room, the use of warmed intravenous fluids, overhead radiant heaters, hot air covers and more recently warming intravascular catheters [16, 43, 44].

Surgery should stop and the patient should be rewarmed if the core temperature drops below 36 °C.

Once the patient is physiologically prepared and the surgical plan has been communicated to the surgical team with a thorough briefing and surgical checklist, the surgery in itself proceeds. The surgical team usually accounts for a team of four to six surgeons, two anaesthetists, one operating department assistant and four nurses.

Following skin preparation with Chlorhexidine or Iodine solutions and draping of the patient, the areas to be debrided and the donor sites are infiltrated in a tumescent fashion with Normal saline and Adrenaline 1:1,000,000.

The debridement then proceeds with the surgeon's technique of choice that may include sharp debridement with hand held or air/electricity powered Dermatomes or other techniques like hydrosurgery systems [45].

Once debridement has been completed and haemostasis achieved, the harvesting of donor sites follows. The skin grafts are then meshed and fixed to the wound bed with staples, suture material or fibrin glue. The skin grafts can be used on their own or combined with allograft or dermal templates.

The surgical procedure may be halted by excessive blood loss, hypothermia, acidosis or physiological instability of respiratory or metabolic sources. Close communication with the anaesthetic team is crucial.

The post-operative period continues in the intensive care unit.

Even though most trauma patients get a single 'hit' followed by predictable recovery phase, Burns patients receive recurrent 'hits' from the onset of the hypermetabolic state, the burn wound toxicity, repeated surgical procedures, dressing changes and showers.

In addition to the physical trauma, burns patients suffer the added psychological trauma of social deprivation due to disfiguring scars, prolonged reconstructive surgery and often a traumatic history with difficult family backgrounds.

The role of the multidisciplinary team is to facilitate the reintegration of burn victims as active and functional members of society.

10.4 Modulation of the Hypermetabolic Response to Burn Injury

Severe burns lead to marked hypermetabolism and catabolism, which is associated with morbidity and mortality. This hypermetabolism leading to catabolism can be modulated by non-pharmacological measures such as early enteral feeding, warm environment, early excision and wound closure with meticulous infection control.

10.4.1 Nutrition

The nutritional impact of burn injury in the critically ill burned patient is clearly seen in the failure of the oral diet due to the potential presence of an altered level of consciousness and gastrointestinal dysfunction. This leads to weight loss, wound healing and multiorgan failure.

Loss of lean body mass of 10 % will impair the immune function and a 40 % loss will lead to death as a result of massive catabolism [46].

The early delivery of nutrients via a naso-jejunal tube and the insertion of a naso-gastric tube as a marker of sepsis ensures the avoidance of bacterial translocation in the gut and helps in abating the hypermetabolic response to burn injury.

10.4.2 Pharmacological

Two of the most used pharmacological strategies to modulate hypermetabolism are beta-blockade with Propranolol and the use of the anabolic steroid Oxandrolone.

Blockade of β-adrenergic receptor affects cardiac work, resting energy expenditure, lipid metabolism and bone formation [47]. The usual dose of 1 mg/kg/day decreases thermogenesis, lowers heart rate, increases lean body mass and decreases exogenous insulin requirements.

Oxandrolone, at a dose of 10 mg twice a day, reduces skeletal muscle protein degradation and improves protein synthesis in both males and females during the acute phase after major burns. It also improves donor site wound healing and decreases weight loss and the length of acute hospital stay [48].

10.5 Conclusion

There are few surgical specialties in which the patient can so clearly benefit from the input of a myriad of professionals concentrated in a resource-rich hub of expert care. The careful application of principles of trauma management with attention to the assessment to the burn depth and size, fluid resuscitation, early debridement and wound cover and the modulation of the hypermetabolic response to burn injury ensures positive outcomes and a successful return of the burn victim to society.

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The Critically Ill Burn Patient: How Do We Get It Right?

11

Katherine Horner, Catherine Isitt, and Asako Shida

Summary of Abbreviations

ARDS	Adult respiratory distress syndrome
BAL	Bronchoalveolar lavage
BICU	Burns intensive care unit
DIC	Disseminated intravascular coagulation
IL	Interleukin
LOS	Length of stay
PGE_2	Prostaglandin E_2
ROS	Reactive oxygen species
TBSA	Total body surface area
TNF-α	Tumour necrosis factor alpha
VTE	Venous thromboembolism

11.1 Introduction

Significant advances have been made in burn care over recent decades. Traditionally, the Baux score was used to predict mortality after burn injury (age in years plus percentage body burn equated to percentage mortality) however, this scoring system is now too pessimistic. Today, young adults with 76 % total body surface area (TBSA) burns have a 50 % chance of survival [1]. Nevertheless, burns >30 % TBSA, as well as age over 60 years and presence of inhalation injury, are strong predictors of mortality [2].

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_11

The management of patients with severe burns is complex, with many unanswered questions regarding best practice. Effective burn shock resuscitation, early surgical intervention, attention to infection control and treatment by a multidisciplinary team in a specialized burn centre improves clinical outcome [3–5] (Table 11.1).

Burn centres treat the highest level of injury and have discrete, separately staffed, critical care facilities with immediate access to an operating theatre. Adult patients will be admitted to a burn centre if the TBSA is ≥40 % or ≥25 % with inhalation injury. Adult patients should be discussed with a burn centre in the following circumstances [6]:

- Burns ≥25 % TBSA (especially patients aged > 65 years or with significant co-morbidity)
- Patients considered for end-of-life care as a result of burn injury
- Suspicion or presence of inhalation injury
- Actual or anticipated need for HDU/ITU care
- Presence of major trauma in addition to burn injury

11.2 Airway Management

Thermal injury to the oral cavity and throat can cause oedema of the supraglottic airway, leading to airway obstruction and difficulties with intubation. Patients with burns to the neck are also at risk of airway obstruction due to external compression from oedema and eschar. Maximal oedema typically occurs 8–36 h after the burn injury [7, 8].

Indicators of upper airway burn injury include hoarse voice, carbonaceous sputum, singed nasal hairs, facial burns and/or history of confinement in a burning environment; however, these signs are not sensitive or specific [7]. Clinicians tend to have a low threshold for early tracheal intubation in patients with possible upper airway burn injury, due to valid concerns about impending airway obstruction. It is important to remember, however, that tracheal intubation is not risk free and the majority of patients who are intubated for suspected upper airway burn injury do not actually have it [7]. Intubation should not be performed solely for facial burns [4, 7].

Continuous assessment (especially with regard to voice quality), serial examinations of the intra-oral mucosa (looking for evidence of oedema or blistering) and serial fibreoptic nasendoscopies may be the most accurate way of detecting those at risk of airway obstruction [7, 8]. Upright positioning and avoidance of over-zealous fluid resuscitation will minimize facial and airway oedema [7–9]. The regional burn centre is always available to advise about the management of patients with suspected upper airway burn injury [6].

If tracheal intubation is performed, it is important to leave the endotracheal tube uncut, as massive facial oedema can develop. The initial intubation should be with a size 8.0 mm internal diameter endotracheal tube or larger, as this allows passage of a standard bronchoscope and facilitates investigation and treatment of inhalation injury [9]. Once facial and airway oedema occur, it can be difficult and risky to upsize a small endotracheal tube.

Table 11.1 Summary of critically ill burn patient care

Aspect of care	Acute management	Ongoing management
Airway	Assess airway involvement Intubate with ≥size 8 mm, uncut ETT if necessary Upright positioning Escharotomy of neck burns to prevent external airway compression	Early extubation of those without airway involvement or inhalation injury Early tracheostomy to facilitate weaning, suctioning and multiple surgical interventions
Breathing	Bronchoscopy to assess inhalation injury Therapeutic BAL to remove soot and debris Commence nebulised heparin Escharotomy and debridement of chest burns to prevent chest wall compression	Lung protective ventilation strategy VAP prevention Surveillance and treatment of pneumonia Serial BAL to remove mucus/debris if necessary Nebulised N-acetylcysteine and dornase alfa Chest physiotherapy
Circulation	Fluid resuscitation according to Parkland Formula Avoid fluid over-resuscitation Aim 0.5–1 mL/kg/hr urine output Vasopressors/inotropes as required	Careful assessment of fluid balance Avoid fluid overload Aim 0.5–1 mL/kg/hr urine output Vasopressors/inotropes as required Consider propranolol to attenuate the hypermetabolic state
Pain Management	Multimodal analgesia Ketamine, opioids, paracetamol	Flexible, multimodal analgesia Ketamine, clonidine, opioids, paracetamol Early initiation of amitriptyline and pregabalin General anaesthesia/deep sedation for extensive dressing changes
Nutrition	Enteral feeding within 24 h of injury High protein feed	Early involvement of a dietician Enteral feed via a nasojejunal tube is preferable to a nasogastric tube Consider parenteral nutrition if not tolerating enteral feed after aggressive use of promotility agents Supplementation with vitamin C, vitamin E and trace elements Insulin sliding scale to control blood glucose Prophylactic PPI Consider oxandrolone

(continued)

Table 11.1 (continued)

Aspect of care	Acute management	Ongoing management
Haematology	Assess and correct coagulopathy before surgical intervention Ensure blood cross-matched for surgical intervention	Maintain Hb > 70 g/L Prophylactic LMWH
Infection	Early excision and debridement of wounds Aim for early wound closure	Aggressive attention to infection control Regular wound checks Regular wound debridement Silver sulfadiazine dressings Regular screening for organisms (wounds, sputum, urine)

11.3 Inhalation Injury

Smoke inhalation is a major cause of morbidity and mortality in burn patients. A dose dependent relationship between degree of smoke exposure and severity of airway injury has been described [10].

Smoke inhalation directly damages the airways, causing exfoliation of the epithelial lining, mucus secretion, inflammatory cell influx and plasma exudation. Intra-airway coagulation and fibrin deposition occurs, which admixes with cellular debris and mucin to form obstructive airway casts. The obstructive airway casts partially or totally obstruct the lower airways leading to gas trapping, alveolar barotrauma, ventilation/perfusion mismatch and the development of pneumonia [10].

Care for patients with inhalation injury includes a lung protective ventilation strategy, serial bronchoalveolar lavage (BAL) to clear soot, casts and mucus plugs, and attention to preventing and treating pneumonia. BAL samples can be subjected to quantitative microscopy, with 10^4 CFU/mL diagnostic for pneumonia [11].

Treatment with inhaled heparin potentiates anti-thrombin III and prevents the formation of fibrin. It should be initiated as soon as possible, and administered every 4h for 48 h. Adding mucolytic oral carbocisteine and nebulized N-acetylcysteine further minimizes the formation of obstructive airway casts. Inhaled dornase alfa, which cleaves DNA in mucus, might augment the breakdown of cellular debris [10, 11].

Patients with inhalation injury are at risk of systemic toxicity from inhaled carbon monoxide or hydrogen cyanide. These molecules impair the delivery and utilization of oxygen leading to tissue hypoxia. Patients with carboxyhaemoglobin levels above 10 % should be treated with 100 % oxygen. Whilst hyperbaric oxygen therapy may be beneficial, it is logistically difficult to achieve. Treatments for cyanide poisoning include sodium thiosuphate and sodium nitrite [8].

11.4 Burn Shock

Patients with burns of >15 % TBSA require fluid resuscitation to avoid hypovolaemic shock [5, 12, 13]. Burns involving >30 % TBSA are only partially responsive to fluid therapy as the systemic inflammatory response causes microvascular injury, fluid shifts, vasodilatation, decreased cardiac contractility and decreased cardiac output [5, 14]. Inotropic/vasopressor support may be required if hypotension persists despite fluid replacement [15], although vasoconstriction may extend the burn injury.

There is no consensus on the most effective fluid resuscitation solution or volume. Worldwide, the Parkland Formula is the most commonly used formula and Ringer's Lactate solution the most commonly used fluid, although colloid is often initiated within the first 24 h of injury [16]. Colloids, including albumin, may reduce oedema-related complications and be warranted in patients with the most severe burns (>40%TBSA) [5, 16].

There is a tendency for patients to receive more fluid than they require, both in the initial resuscitation and ongoing management phases [16–18]. Common

problems are for medical staff to inaccurately assess the size of the burn [19], lose track of the amount of fluid delivered or neglect to reduce fluid input in the face of a high urine output. Over-resuscitation is not benign, causing coagulopathy [18, 20], oedema, compartment syndromes and ARDS [15, 16]. It also impacts on the success of skin grafting.

Whilst the Parkland Formula is a useful initial guide, fluid therapy should ideally be 'goal directed'. The most commonly used parameter to guide fluid therapy is urine output, aiming for 0.5–1 mL/kg/h [16]. Computer controlled feedback technology that automatically controls infusion rates in response to urine output has been developed [21]. This technology may reduce crystalloid infusion volumes [22].

Other units use invasive and non-invasive cardiac output monitoring to dictate fluid and inotrope/vasopressor therapy [16]. In a small study, LiDCO reduced fluid administration and decreased cumulative fluid balance compared with standard monitoring [23].

Oxidative stress is a key component of the systemic inflammatory response and contributes to burn shock. Antioxidant vitamin C has been investigated as a treatment. Matsuda and Tanaka administered high-dose vitamin C to animals and humans and found a decrease in volume of resuscitation and compartment syndromes. Further studies are needed to evaluate efficacy and determine the optimum dose and route of administration, and whether any side effects occur [24].

Other researchers are investigating the use of extra-corporal blood circuits to modulate the inflammatory response in the early post-burn period, either with cytokine removing membranes or continuous venovenous haemofiltration. Both have shown promising results in terms of reducing cytokine levels, catecholamine requirements, ARDS and mortality, albeit in small studies. Further evaluation is warranted [25].

11.5 Hypermetabolic State

After the first 24–48 h of injury, patients with severe burns enter a hypermetabolic and catabolic state, characterized by hyperdynamic circulation, hyperthermia, hyperglycaemia and rapid muscle wasting. These responses are seen in all surgical and trauma patients, however, the severity and persistence is unique to burn patients. The response is driven by marked and sustained sympathetic stimulation and inflammation, causing catecholamine, glucocorticoid, glucagon, dopamine and cytokine release, particularly IL-6, IL-8, G-CSF and MCP-1. This hypermetabolic state persists for many years after the initial burn injury [26].

Loss of lean body mass after burn injury impairs immune function and wound healing, contributes to the hyperglycaemic state, increases the risk of pressure sores, prolongs mechanical ventilation and increases mortality [26].

Alongside good nutritional support, physiotherapy and early wound closure, some pharmacological therapies may be beneficial in blunting this hypermetabolic and catabolic response, and may preserve muscle mass [5, 26]. Oxandrolone is a testosterone analogue, which enhances protein synthesis and reduces lean mass catabolism. It has been shown to reduce length of stay (LOS) in patients with >20 % TBSA burns [27, 28]. The non-selective beta-blocker propranolol blocks the effects

of the catecholamine surge and has been shown to suppress lipolysis, decrease resting energy expenditure, preserve lean body mass and decrease LOS [29].

Hyperglycemia in burn patient populations is associated with stimulation of a persistent inflammatory state, poor wound healing, increased skin graft loss, protein catabolism, infection and death [26, 29]. Studies in both children and adults have shown that controlling blood glucose to a target range of 4–7.5 mmol/L improves morbidity and mortality [30, 31].

11.6 Pain Management

Burn injury induces excruciating pain, which is poorly understood and challenging to control. Poorly controlled pain in the acute setting causes distress and lack of engagement with treatment, and leads to chronic pain and post-traumatic stress disorder [32].

Burn tissue damage is caused by direct thermal injury, ischaemia and the inflammatory response. Sensory and sympathetic neurons are activated, sensitized and/or directly injured causing a combination of nociceptive and neuropathic pain [32–34]. Repeated painful insults, such as dressing changes or surgery, cause central sensitization and promote chronic pain development [33, 34].

Burn patients experience background pain, breakthrough pain, procedural pain and post-operative pain [32, 33]. The analgesic regimen should be multimodal, continuously assessed and flexible to meet patients' varying needs. Early involvement of the pain team is crucial [35].

The usual mainstay of treatment is opioids, but opioids alone are not sufficient [32, 33, 35]. The prolonged requirement for opioids by burn patients leads to tolerance and significantly increased doses. Paracetamol, ketamine and clonidine are useful adjuncts to opioids. Pregabalin and amitriptyline should be initiated early for the neuropathic pain component [35]. Regional anaesthetic techniques can be considered, but are often not useful due to coagulopathy, concerns about infection and the extent of the wounds [33, 35]. General anaesthesia, or deep sedation by an anaesthetist, is often warranted for procedures such as dressing changes [33].

Alterations in the magnitude or type of pain should be fully assessed, as they may indicate the development of burn complications such as wound infection, compartment syndrome or intra-abdominal pathology [33].

11.7 Nutrition

Nutritional support is an essential component of burn care. Failure to meet the nutritional requirements of the catabolic burn patient leads to impaired wound healing, susceptibility to infection, development of pressure sores, organ failure and death [5, 26, 36].

The evidence favours enteral over parenteral feeding [5] and it should be commenced as soon as practical. Improved outcomes have been seen when enteral nutrition is initiated <24 h after burn injury [37, 38]. At our institution, a nasogastric tube for enteral nutrition is inserted at the earliest opportunity and converted to a

nasojejunal (NJ) tube when trained staff are available. Feeding via the NJ tube removes the requirement for 'starvation periods' prior to theatre and significantly increases the amount of nutrition delivered. As NJ tubes easily become blocked, it is useful to deliver medication via an NG tube and use the NJ tube solely for feed. Parenteral nutrition should be considered if patients are not tolerating enteral feed despite aggressive attempts to maximize gastrointestinal motility.

Burn injury triggers severe inflammatory derangement and the generation of reactive oxygen species (ROS). Supplementation with antioxidant vitamin C and E has been advocated to help prevent cellular injury from ROS. Furthermore, various enzymes defend the body against ROS, and these enzymes require the cofactors zinc, manganese, iron and selenium. Results from small studies show that supplementing burn patients with trace elements reduces hospital stay and decreases pulmonary infections. Selenium may be particularly valuable [36]. The best route, dose and combination of trace elements and vitamins is not yet known. Caution should be exercised in patients with renal failure [36].

11.8 Curling's Ulcer

Burn patients are at significant risk of developing gastric ulcers, particularly ulceration of the proximal duodenum (Curling's Ulcer). Optimizing gut perfusion, early enteral feeding and use of proton pump inhibitors significantly reduces the rate of gastrointestinal ulceration [5].

11.9 Haematology

A number of coagulation derangements occur in patients with major burns. A coagulopathy often develops within hours of burn injury, the likelihood of which increases with burn size and presence of inhalation injury [18, 39]. The precise pathophysiology is unclear. It may represent cytokine mediated activation of the protein C pathway analogous to that seen in major trauma patients [39], a dilution coagulopathy secondary to fluid resuscitation [18] or disseminated intravascular coagulation (DIC) [40], although the incidence of DIC is thought to be low [18, 41]. Whatever the mechanism, the presence of early coagulopathy is an independent risk factor for morbidity and mortality [18, 39]. Recognition and management is essential, as it will influence blood loss and transfusion requirements during early wound excision. Thromboelastography, in addition to laboratory tests, is useful in determining the cause and treatment of the coagulopathy [39].

Later in the clinical course, patients develop risk factors for venous thromboembolism (VTE). Patients often become hypercoagulable and have prolonged periods of immobilization, due to the presence of large wounds with restrictive dressings, the need for sedation and analgesia, and the multiple trips to theatre. Despite these risk factors, the actual incidence of VTE is low [42]. Nevertheless, initiating pharmacological VTE prophylaxis is prudent.

The optimal transfusion trigger in burn patients is uncertain. The Transfusion Requirements in Critical Care (TRICC) study [43], which found that a restrictive

blood transfusion strategy (maintaining Hb 70–90 g/L) was at least as safe as a liberal strategy (maintaining Hb 100–120 g/L), only included a small proportion of trauma patients, did not evaluate effect on wound healing and may not apply to the burn population. Critically ill burn patients differ enormously from patients in general critical care units, as they have extensive wounds and often require multiple surgical procedures with the potential for major haemorrhage. Commencing surgical wound excision with a low starting haemoglobin concentration could be unwise [5].

A 2004 review of burn centre transfusion practices in the United States showed that for patients with burn injury >20 % TBSA, the initial transfusion trigger was 93.5 g/L [44].

Nevertheless, limited data suggests that a transfusion trigger of 70 g/L compared to 90 g/L is safe and may be beneficial [45, 46]. The American Burn Association is currently conducting a prospective randomized trial comparing restrictive versus liberal blood transfusion to help clarify this issue.

11.10 Microbiology and Sepsis

All patients on a burns intensive care unit (BICU) will require antibiotics at some point in their treatment. Approximately 44 % of patients develop pneumonia, 22 % a urinary tract infection, 11 % a blood stream infection and less than 1 % develop sepsis from the burn wounds themselves [47].

Critically ill burn patients are particularly susceptible to infection due to loss of skin integrity, the presence of invasive devices, the prolonged need for mechanical ventilation and the fact that thermal injury causes immunosuppression. The initial burn injury stimulates the innate immune response with the release of pro-inflammatory cytokines. However, continued upregulation of PGE_2 by IL1β and TNF-α ultimately has a suppressive effect on T-cell differentiation and causes anti-inflammatory cytokine production. Overactivation of the complement cascade further contributes to immunosuppression. C5a in particular inhibits leukocytes [11].

Burn wound tissue provides a medium for bacterial growth, and is often colonized with multidrug resistant pathogens, which can then seed elsewhere [34, 47]. In the first 48 h post injury, colonization of burn wounds is with the native Streptococcus originating from deep sebaceous glands. Bacteria from the gut, upper respiratory tract and hospital environment are next to colonize [48]. Burn-induced changes to the gut mucosa results in bacterial translocation of Gram-negative and Enterobacteriaceae pathogens (e.g. *Pseudomonas aeruginosa, Klebsiella* spp., *Serratia marcescens, E. coli* and *Acinetobacter baumannii*). These pathogens are notable for their increasing resistance to a broad range of antimicrobial agents. Later, fungal colonization occurs, generally after broad-spectrum antibiotic use. *Candida albicans* is the most common pathogen and remains broadly sensitive to Fluconazole; however, there is a trend towards resistant *Candida* spp. such as *Candida glabrata* and *Candida krusei*, which may require treatment with Voriconazole or Caspofungin [11].

The low incidence of burn wound related sepsis is due to the practice of early surgical excision and wound closure. Patients also undergo frequent debridement with warm water and chlorhexidine. Once the wounds are clean, they are treated with a topical antimicrobial, such as silver sulfadiazine. Regular wound swabbing

determines which pathogens are present, along with their antibiotic sensitivities. Antibiotics should only be given if clinical signs of infection develop, i.e. cellulitis, changes in wound colour, conversion of partial thickness to full thickness injury, graft loss or a systemic response consistent with sepsis [11, 48].

The diagnosis of sepsis in burn patients is extremely challenging, because signs of sepsis (elevated temperature, tachycardia, tachypnoea and leukocytosis) are present in the burn patient without infection. The American Burn Association has published burn-specific sepsis criteria [49]. If three of the criteria are met, the clinician should consider the presence of a clinically significant infection and initiate empirical antimicrobial therapy.

Signs of sepsis in burn patients are as follows [49]:

- Temperature greater than 39 °C or less than 36.5 °C
- Progressive tachycardia (>110 beats per minute)
- Progressive tachypnoea
- Thrombocytopenia (platelets <100,000/μL after the first 3 days)
- Hyperglycemia (in the absence of pre-existing diabetes mellitus)
- Inability to continue enteral feed for more than 24 h

Reliable markers of sepsis in burn patients are desperately needed. The most commonly used markers are increasing WCC or CRP, but these may rise due to the burn itself or surgical intervention. Some studies have shown procalcitonin levels to be useful. Levels of 1.5 ng/mL had a sensitivity of 88 % and a specificity of 92 %, and its maximum levels were an independent predictor of mortality [50].

In the past, burn patients were bathed in warm hydrotherapy pools, however, these pools caused bacterial spread between wound sites and were a source of bacterial spread between patients. Today, the predominant source of cross-contamination is healthcare workers, rather than shared equipment. All BICU patients should be nursed in individual rooms and there should be aggressive attention to infection control in order to prevent the spread of increasingly resistant pathogens [11].

Conclusion

How to best care for critically ill burn patients is a rapidly evolving, complex and controversial field. It is hoped that the multiple studies currently underway will answer many of the disputed aspects of burn management and lead to further significant improvements in survival and outcome.

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Venous Thromboembolism Prevention and the Role of Non-Coumarin Oral Anticoagulants in the Intensive Care Units

12

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Summary of Abbreviations

AF	Atrial fibrillation
AES	Anti-embolism stockings
DVT	Deep venous thrombosis
GCS	Graduated compression stockings
HIT	Heparin induced thrombocytopenia
LMWH	Low molecular weight heparin
NOAC	Non-coumarin oral anticoagulants
PE	Pulmonary embolism
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_12

12.1 Introduction

Venous thromboembolism (VTE) is a common and potentially lethal complication in critically ill patients [1, 2]. In comparison with other hospitalised patients, patients in intensive care unit (ICU) have a higher risk of deep venous thrombosis (DVT) as a result of many predisposing factors such as immobilisation, central venous catheterisation, sepsis, trauma, cardiac or respiratory failure, malignancy and increased age [2, 3]. The reported rate of DVT in this category of patients ranges from 15 % to almost 60 % depending on patients' underlying clinical characteristics [4]. Pulmonary embolism (PE) is the most serious clinical complication of DVT and remains one of the most frequent causes of unexpected deaths in hospitalised patients, the incidence at post-mortem being as high as 27 % [5].

Diagnosis of DVT in critically ill patients can be challenging and a significant proportion of cases of peripheral thrombosis go undetected in the intensive care unit [6]. An important contributing factor is that critically ill patients often cannot reliably communicate symptoms due to impaired consciousness from drugs or their underlying illness, and physical signs such as unilateral leg oedema can be absent or missed because these patients are generally supine and frequently already have bilateral oedema [7]. D-dimer levels are usually elevated and cannot be used solely to guide diagnostic testing for VTE. Critically ill patients often develop haematological failure as result of sepsis, malignancy or major trauma and may therefore be susceptible to bleeding complications [8]. Thrombocytopenia is indeed a common finding in intensive care patients and when moderate or severe represents a contraindication for pharmacological thromboprophylaxis [8]. Therefore, individualised risk-benefit assessment is necessary to maximise benefit and minimise harm of VTE prevention in these patients.

12.2 Mechanical Thromboprophylaxis

Mechanical methods of thromboprophylaxis are generally used when pharmacological prophylaxis is contraindicated.

The types of mechanical thromboprophylaxis include the following:

- Anti-embolism stockings (AES) – designed for VTE prevention in the immobile patient
- Graduated compression stockings (GCS) – designed for the management and treatment of conditions such as venous leg ulcers in the ambulant patient
- Foot impulse devices – they increase venous outflow and reduce stasis in immobilised patients via a pumping mechanism in the sole of the foot
- Intermittent pneumatic compression devices – they provide intermittent cycles of compressed air which alternatively inflate and deflate the chamber garments, thus enhancing venous return

A review of 21 studies relating to the use of mechanical thromboprophylaxis in the critically ill showed that neither GCS nor pneumatic compression devices led to a significant reduction in the risk of thromboembolism [9]. Furthermore, no trial of

mechanical thromboprophylaxis has been shown to effectively reduce the risk of death secondary to PE [9]. Mechanical devices appear to act in a synergistic manner when combined with pharmacological thromboprophylaxis [10]. By contrast, in the context of surgery, a large systematic review demonstrated that the use of mechanical compression after surgery reduces the risk of DVT by about two thirds when used as dual therapy and by about half as monotherapy [11]. The suitability of AES should be assessed prior to offering them to patients to exclude any contraindications that may be present, e.g. suspected or proven peripheral arterial disease; peripheral arterial bypass grafting; peripheral neuropathy or other causes of sensory impairment; local conditions in which AES may cause damage, i.e. dermatitis, gangrene and recent skin graft; severe leg oedema or pulmonary oedema from congestive heart failure; unusual leg size or shape or major limb deformity preventing correct fit; cellulitis and known allergy to material of manufacture.

12.3 Pharmacological Thromboprophylaxis

12.3.1 Heparins

The agents currently used in intensive care for pharmacological thromboprophylaxis are unfractionated heparin (UFH) and low molecular weight heparin (LMWH). Heparin binds to and potentiates the activity of antithrombin, which inhibits the activity of the coagulation factors IIa (thrombin) and Xa (activated factor Xa) and to a lesser extent IXa and XIa. Several studies have shown that subcutaneous UFH at a dose of 5000 units 8 hourly is effective for thromboprophylaxis in the critically ill. However, UFH has an inferior safety profile when compared to LMWH, as the first incidence of fatal heparin induced thrombocytopenia (HIT) is ten times that of LMWH [12]. One study comparing UFH to LMWH in 325 medical ICU patients showed that DVT was detected by ultrasound in 16 % of patients receiving UFH compared to 13 % on LMWH, while no differences were noted in the rates of proximal DVT or bleeding [13]. A major limitation of LMWH in the critical care population is the risk of accumulation in patients with renal impairment leading to an unpredictable and excessive anticoagulation. This clearly limits the role of LMWH as thromboprophylaxis in intensive care. Another important issue is related to the use of vasopressors, which could cause impaired peripheral circulation and inadequate systemic bioavailability of LMWH reducing the effectiveness of pharmacological prophylaxis [14]. Studies have shown that critically ill patients receiving vasopressor support had significantly lower anti-Xa levels than those patients not on vasopressors. The underlying mechanism is considered the decreased absorption of LMWH from the subcutaneous tissues due to reduced perfusion caused by the vasopressor [15].

12.3.2 Fondaparinux

An alternative to heparins is fondaparinux. This is a synthetic, highly sulphated pentasaccharide, which has a sequence derived from the minimal antithrombin

binding region of heparin. It binds to antithrombin with a higher affinity than the native pentasaccharide of unfractionated heparin or LMWH and causes a conformation change in the molecule, which dramatically increases its ability to inactivate factor Xa [16]. A particular benefit of fondaparinux is that it does not cause HIT [17]. Similarly to LMWH, fondaparinux is predominantly excreted renally, thus accumulation occurs in renal failure. A meta-analysis of four randomised control trials comparing fondaparinux to enoxaparin in preventing VTE after orthopaedic surgery showed that fondaparinux was more effective compared to enoxaparin by day 11 (6.8 % versus 13.7 %). However, there was significantly more major bleeding episodes in those receiving fondaparinux (2.7 % versus 1.7%; $p=0.008$) [18]. No studies have been conducted using fondaparinux in a critical care population although a study in 849 older acute medical patients versus placebo showed that it is effective in this group and that there was no increased bleeding when compared to placebo [19].

12.3.3 Non-Coumarin Oral Anticoagulants

The field of anticoagulation has changed dramatically with the arrival of oral non-coumarin anticoagulants (NOACs) including an anti-IIa agent (dabigatran) and anti-Xa agents (rivaroxaban and apixaban). These agents are all licensed for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, treatment of DVT/PE and prevention of recurrent DVT/PE and thromboprophylaxis following hip or knee replacement surgery. Table 12.1 summarises the advantages and disadvantages of NOACs compared to LMWH and vitamin K antagonists. Table 12.2 describes pharmacological properties of the NOACs.

12.3.3.1 Rivaroxaban

Rivaroxaban is a selective, short-lived and direct inhibitor of factor Xa. It has a bioavailability of almost 100 % if administered with food and its peak plasma concentrations occur within 2–4 h after oral administration [23, 24]. The half-life of the drug is 5–9 h in young patients and about 11–13 h in the elderly population [25]. Rivaroxaban is predominantly excreted through the kidneys: about 36 % of the drug is excreted unchanged and 30 % is excreted as inactive metabolites; the remaining drug is eliminated in faeces. Rivaroxaban is metabolised via the CYP450 system, primarily through CYP3A4 and CYP2J2 [26]. Therefore, known CYP3A4 inhibitors such as azoles or inducers such as phenytoin will affect its metabolism [26, 27]. Unlike warfarin, rivaroxaban does not require initial bridging with LMWH, and also does not require routine anticoagulation monitoring.

12.3.3.2 Dabigatran

Dabigatran is the only oral direct thrombin inhibitor currently licensed in the UK. It is a selective, short-lived inhibitor of both free and clot bound thrombin. Time to peak plasma concentration after oral intake is 0.5–2 h. Maximum anticoagulant effects are achieved within 1–2 h depending upon food intake with maximum effect in 2 h. Dabigatran etexilate is the prodrug which is converted to the active

Table 12.1 Advantages and disadvantages of low molecular weight heparins (LMWH), novel oral anticoagulants (NOACs) and vitamin K antagonists (VKA)

	LMWH	NOAC	VKA
Advantages	Rapid onset and offset	Oral agent	Oral agent
	Extensive clinical experience	Rapid onset and offset	Extensive clinical experience
	Reliable laboratory measure of anticoagulant activity (i.e. anti-Xa)	Laboratory anticoagulation monitoring not routinely needed (wide therapeutic window)	Reliable laboratory measure of anticoagulant activity (i.e. INR)
	Laboratory anticoagulation monitoring not routinely needed	Fixed dosing	Efficacious reversal agents (e.g. vitamin K, fresh frozen plasma, prothrombin complex concentrate)
	Few drug-drug interactions	Few drug-drug interactions	Safe in renal insufficiency
	Ease of administration (i.e. prefilled syringe)	Few drug-food interactions	
Disadvantages	Parenteral agent	Limited clinical experience	Delayed onset and offset
	Reversal agent (protamine) partially reverses anticoagulant effects	Lack of specific reversal agent (at present)	Many drug-drug and drug-food interactions
	Caution advised in renal insufficiency	Lack of validated laboratory testing of anticoagulant effect	Unpredictable dose requirements and variable dosing
	High level of adherence and compliance required	Caution advised in renal insufficiency	Narrow therapeutic window
		High level of adherence and compliance required	Requires frequent laboratory monitoring

compound dabigatran by non-specific esterases in plasma and liver [28]. Renal excretion of unchanged drug is the predominant elimination pathway, with about 80 % of drug being excreted unchanged in the urine [29]. Dabigatran is not metabolised, induced or inhibited by CYP450 enzyme system. It has a low protein binding (35 %) and is potentially dialyzable. However, because of its large volume of distribution, there is usually a rebound in the drug level; therefore, dialysis as a means of removing the drug from the body is impractical [29, 30]. For management of active bleeding, supportive care and activated charcoal may be given if the patient is seen within 2 h of ingestion of dabigatran.

12.3.3.3 Apixaban

Apixaban is a selective, reversible and direct inhibitor of factor Xa. Food does not interfere significantly with its absorption. Its half-life is 8–15 h. Time to reach

Table 12.2 Pharmacological properties of the NOACs [20–22]

	Dabigatran	Apixaban	Rivaroxaban
Target	Factor II (thrombin)	Factor Xa	Factor Xa
Bioavailability	3–7 %	50 %	66 % without food Almost 100 % with food
Prodrug	Yes (dabigatran etexilate)	No	No
Protein binding	35 %	87 %	92–95 %
Time to maximum concentration (t_{max})	0.5–2 h	3–4 h	2–4 h
Half-life ($t_{1/2}$)	12–17 h	8–15 h	5–9 h (young) 11–13 h (elderly)
Renal elimination	80 %	25 %	66 %
Liver metabolism: CYP3A4 involved	No	Yes (elimination; minor CYP3A4 contribution)	Yes (elimination)
Drug interactions	P-glycoprotein	CYP3A4 P-glycoprotein	CYP3A4 P-glycoprotein

maximum plasma concentration is 3–4 h. It is metabolised by the CYP3A4 in the CYP450 system. Apixaban is approximately 87 % protein bound and is therefore difficult to dialyze [31]. Renal excretion of the active drug is 25 %. Slower excretion is expected in the setting of chronic kidney disease (CKD). Although there has been concern regarding cumulative toxicity in renal insufficiency, however, it has been used successfully with no major increase in bleeding complications in CKD stage III patients [32]. Apixaban seems to have a favourable pharmacokinetic and pharmacodynamic profile compared to the other NOACs. It is minimally excreted through kidneys and has a short half-life. Meta-analysis and indirect comparisons for the safety and efficacy of the three anticoagulants showed apixaban safer than others secondary to less major bleeds [33, 34]

12.3.3.4 Drug-Drug Interactions with the NOACs

Although the NOACs have significantly fewer drug-drug interactions, compared to VKAs, drugs that strongly affect the CYP3A4 enzyme and/or P-glycoprotein can alter the plasma concentration of the NOACs and may lead to clinically significant changes in the anticoagulant effect [27]. CYP3A4 is a member of the hepatic cytochrome P450 enzyme and is responsible for oxidative metabolism of both apixaban and rivaroxaban [35]. Dabigatran etexilate, the prodrug, is metabolised by esterases in the plasma and liver without significant involvement of CYP3A4 [20, 26, 36]. Rivaroxaban and apixaban, substrates of CYP3A4, can act as both inducers and inhibitors leading to potentially increased toxicity or decreased efficacy [35].

P-glycoprotein, an ATP-dependent efflux transporter, mediates drug absorption and excretion. P-glycoprotein is present in many normal human tissues, most notably the luminal membrane of enterocytes and the apical membrane of both hepatocytes and renal tubular cells [36]. P-glycoprotein is responsible for the efflux of

drugs into the biliary canaliculi and renal tubules, decreasing net absorption via increased excretion of drug into the bile and urine [24]. Dabigatran etexilate, rivaroxaban and apixaban (substrates of P-glycoprotein) are susceptible to strong inhibitors or inducers of this transporter.

Commonly prescribed drugs in critical care may interact with the NOACs and are summarised in Table 12.3.

12.3.3.5 Measurement of Anticoagulant Effect and Interpretation or Routine Clotting Tests with NOACs

One of the primary advantages with the NOACs is that routine anticoagulant monitoring is not required as these drugs have predictable pharmacokinetics. The quantitative assessment of the anticoagulant exposure and effect may be required in emergency situations, e.g. bleeding, emergency surgery, renal or hepatic insufficiency, potential drug-drug interactions, suspected overdosing or a new thrombosis develops whilst anticoagulated.

It is paramount to find out exactly when the NOAC dose was last administered and time of blood sampling for accurate interpretation of the coagulation assay and assessment of anticoagulation effect. The maximum NOAC effect on the clotting test will occur at its peak plasma concentration, which is approximately 3 h after ingestion for each NOAC agent. For a blood sample taken at 3 h after NOAC ingestion (peak level), the coagulation assay will show a larger impact on the coagulation compared to a trough level taken at 12 h or 24 h after ingestion.

Dilute thrombin-based assays are available for determination of plasma concentrations of dabigatran [37]. The activated partial thromboplastin time (aPTT) can be used as a crude estimate of the relative intensity of anticoagulation for dabigatran (curvilinear dose-response relationship) but some patients with therapeutic concentrations may have a normal aPTT; results need to be interpreted with caution as sensitivity is variable [37, 38]. A normal thrombin time (TT) generally indicates that dabigatran levels are very low [39]. Anti-Xa chromogenic assays are also available to determine plasma concentrations of apixaban and rivaroxaban [40]. The prothrombin time (PT), has higher sensitivity than aPTT, can be used as an approximate estimation of the intensity of anticoagulation for rivaroxaban (and likely for other factor Xa inhibitors), although some patients with therapeutic concentrations will have a normal PT and aPTT [41]. The anti-Xa chromogenic assay can be used to evaluate the anticoagulation effect of the factor Xa inhibitors, but requires calibration with drug-specific reagents as different assays have different dynamic reagents. For apixaban, both PT and aPTT are insensitive; therefore, the use of routine clotting screen is not informative [42].

12.4 Management of Bleeding Events

Critically ill patients in intensive care often present with coagulopathy and bleeding disorders as a result of multiple factors including activation of inflammatory pathways, consumption of coagulation factors and dilutional changes. There is no

Table 12.3 Drug-drug interactions with NOACs [20–22]

Drug	Via	Dabigatran	Apixaban	Rivaroxaban
Amiodarone	P-glycoprotein inhibitor	Use with caution and monitor for signs of bleeding or anaemia (particularly in renal impairment) *Increases dabigatran plasma concentrations*	Use with caution *Moderate increase in apixaban plasma concentration*	No data
Digoxin	P-glycoprotein	No effect	No effect	No effect
Diltiazem	Moderate CYP3A4 and weak P-glycoprotein inhibitor	No effect	Use with caution *Moderate increase in apixaban plasma concentration*	No effect
Dronedarone	Strong P-glycoprotein inhibitor	Contraindicated/ Not recommended	No data	Not recommended due to limited clinical data
HIV protease inhibitors, e.g. Ritonavir	Strong CYP3A4 and P-glycoprotein inhibitors	No data yet (not recommended)	Contraindicated/not recommended *Increases apixaban plasma concentrations*	Contraindicated/not recommended *Increases rivaroxaban plasma concentrations*
Ketoconazole Itraconazole Voriconazole Posaconazole	Strong CYP3A4 and P-glycoprotein inhibitors	Contraindicated/Not recommended *Increases dabigatran plasma concentrations*	Contraindicated/not recommended *Increases apixaban plasma concentrations*	Contraindicated/not recommended *Increases rivaroxaban plasma concentrations*
Rifampicin Carbamazepine Phenytoin	Strong CYP3A4 and P-glycoprotein inducers	Contraindicated/Not recommended *Decreases dabigatran plasma concentrations*	Use with caution for AF Not recommended for VTE treatment (efficacy compromised) *Decreases apixaban plasma concentrations*	Avoid/not recommended unless closely monitored as efficacy compromised *Decreases rivaroxaban plasma concentrations*

specific antidote for the NOACs at present to reverse anticoagulant effect/bleeding with NOAC [43]. However, the outcome in patients with intracranial haemorrhage-was no worse in patients taking dabigatran than in those taking warfarin. Similar results have been reported with rivaroxaban [44, 45].

12.4.1 Non-Life-Threatening Bleeding

Standard supportive measurements are recommended, e.g. mechanical compression, surgical haemostasis, fluid replacement and other haemodynamic support. NOACs have relatively short elimination half-lives. After cessation of NOAC, restoration of haemostasis is to be expected within 12–24 h after the last ingested dose, given that the plasma half-life of the NOACs is around 12 h.

Red cell and platelet transfusions may be given if necessary. Fresh frozen plasma may be administered as a plasma expander, but not as a reversal agent as it is unlikely to be effective [24, 46, 47].

For patients on dabigatran, adequate diuresis should be maintained and dialysis may be considered as an option.

12.4.2 Severe or Life-Threatening Bleeding

It is important to consult haematology for an individualised plan for critical ill patients requiring management of bleeding events. Intracerebral haemorrhage or haemorrhage in a critical organ (e.g. ocular) warrants immediate attempts to neutralise the anticoagulant effect of the NOAC, by either administration of activated prothrombin complex concentrate factor VIII inhibitor bypassing activity (FEIBA) 30–50 units/kg or prothrombin complex concentrate 50 units/kg, possibly re-administered once at an 8-h interval [47, 48]. Activated charcoal may be used to decrease absorption of dabigatran in patients with a suspected overdose or bleeding event, but to be effective should be given within 2 h after the last ingested dose [49]. The use of other procoagulants such as antifibrinolytics, e.g. tranexamic acid or desmopressin, may be considered; however, there is no clinical data on their effectiveness in NOAC-associated bleeding.

12.5 Summary

The NOACs are currently not licensed for thromboprophylaxis in medical and surgical hospital inpatients; therefore, LMWH still represents the first-line agent for thromboprophylaxis. The lack of a specific antidote to reverse NOAC-anticoagulant effect at present is certainly an important limitation. It is likely that the availability in the near future of specific antidotes and rapid coagulation assays to determine the plasma levels of the NOACs will improve management of patients with serious or life-threatening bleeding leading to a safer use of these drugs in critically ill patients.

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Magnesium and Cell Membrane Stability in the Critically Ill Patient

13

Felicia Bamgbose and Pranev Sharma

Summary of Abbreviations

ACE	Angiotensin converting enzyme
ATP	Adenosin triphosphate
BNF	British National Formulary
IMM	Inner mitochondrial membrane
MPTP	Mitochondrial permeability transition pore
NMR	Nuclear magnetic resonance
PTH	Parathyroid hormone

13.1 Introduction

Normal serum magnesium (Mg^{2+}) reference range is 0.7–1.1 mmol/L, of which 65–80 % is ionised and considered to be the physiologically useful portion in serum [1–4].

The remaining magnesium is protein bound or complex bound. Although magnesium is not part of a routine electrolyte screen in hospital practice, it is very important that magnesium levels in patients are not overlooked. It has been estimated that 65 % adult and 30 % neonatal intensive care patients have hypomagnesaemia, compared to 7–11 % of general hospital inpatients [4, 5]. As few as 10 % patients with hypomagnesaemia have magnesium requested on their blood tests [4]. This is significant because hypomagnesaemia causes a wide variety of signs and

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_13

Table 13.1 Symptoms of hypomagnesaemia

Cardiovascular	Neuromuscular	Electrolyte disturbance	Other
ECG changes	Muscle weakness and fatigue	Hypokalaemia	Nausea and vomiting
Cardiac arrhythmias	Hyperreflexia	Hypocalcaemia	Migraine
Heightened digitalis toxicity	Tremors		Anorexia
	Positive Chvostek's and Trousseau's signs		
	Seizures and coma		

symptoms, which are illustrated in Table 13.1 and discussed in more detail later in this chapter.

Signs are not seen until serum Mg^{2+} falls below 0.5 mmol/L, but this is very variable [4]. Hypomagnesaemia may also cause complications including lactic acidosis [6] and electrolyte imbalances, particularly hypocalcaemia and hypokalaemia due to altered parathyroid hormone (PTH) handling and urinary wasting, respectively [7–9].

Hypomagnesaemia in critically ill patients has been linked to increased morbidity and a decrease in survival time prior to death, with worse averages on prognostic scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) II [10]. Considering the risks associated with low magnesium and the lack of specific signs and symptoms, it is important to maintain a high level of suspicion for low magnesium, particularly in susceptible individuals such as those with history of alcohol abuse, diabetes and chronic diarrhoea [6, 9]. Hypermagnesaemia has a far lower prevalence amongst patient populations. The pathophysiology is commonly iatrogenic, so will be examined in Sect. 13.7.

13.2 Normal Physiology of Magnesium

Magnesium homeostasis is achieved via renal excretion, gastrointestinal absorption and bone resorption. Total magnesium body contents are approximately 22–26 mg [4], which is distributed between bone (53 %), muscle (27 %), soft tissue (19 %) and blood (0.3 %) [5]. Second only to potassium as the cation with highest intracellular concentration of 14–20 mM [3], magnesium has several important cellular roles and is a cofactor for over 300 enzymes, including ATPases and adenylate cyclase. A variety of different mechanisms are employed to achieve this function, such as substrate binding, initiating conformational changes, complex aggregation and binding directly to the active site of an enzyme. This gives magnesium an important role in protein synthesis, metabolic reactions and in the cell cycle. It is functionally vital for the cell, providing stability for nucleic acids, proteins and cell membranes [3, 7, 11].

An example of magnesium's physiological importance is its role in mitochondrial membrane stability; magnesium protects mitochondria from formation of the permeability transition pore, as illustrated in Fig. 13.1.

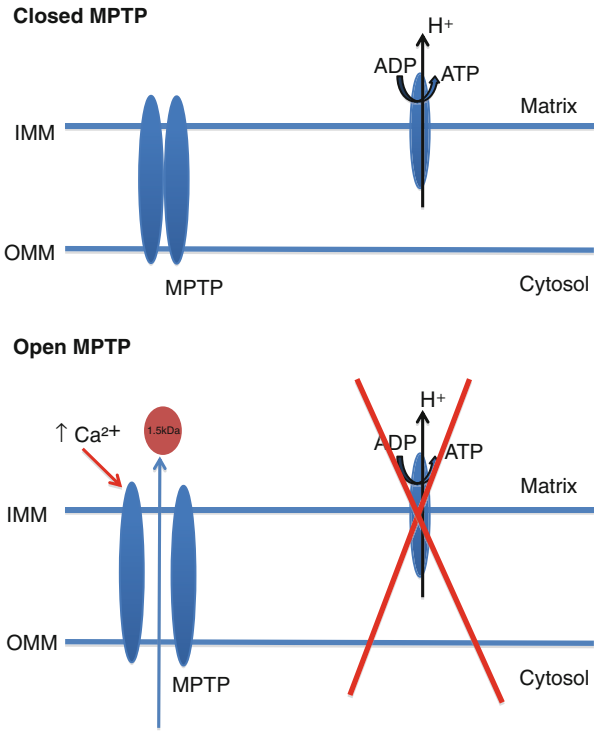

Fig. 13.1 The mitochondrial permeability transition pore (MPTP)

The inner mitochondrial membrane (IMM) is a barrier to regulate entry of molecules into the matrix. Oxidative phosphorylation relies on a positive proton gradient and enables formation of ATP.

Increased mitochondrial calcium can trigger pore formation, enabling molecules to pass into the matrix and disrupting oxidative phosphorylation.

Opening of the pore allows any molecule less than 1.5 kDa to cross the normally tightly regulated inner mitochondrial membrane, causing the mitochondria to swell. Subsequently this leads to cellular necrosis due to uncoupling of oxidative phosphorylation in the mitochondrial inner membrane. Alternatively, if the pore subsequently closes, the cell will undergo apoptosis mediated by cytochrome C and other pro-apoptotic molecules, which are released from the damaged outer membrane [12]. Increased levels of mitochondrial calcium can trigger pore formation, which is hindered by elevated extracellular magnesium [12]. One of the proposed mechanisms for this is via inhibition of L-type calcium channels by magnesium, preventing the rise in intracellular and mitochondrial calcium [13].

Magnesium also antagonises calcium in muscle function, neurotransmitter release and cardiac contractility [4, 14]. It has been proposed that magnesium antagonises calcium at the ryanodine receptors of cardiomyocytes by competitively inhibiting calcium activation sites at low calcium ion concentrations and by inhibition at the calcium ion inhibition site at high calcium ion concentrations, resulting in decreased

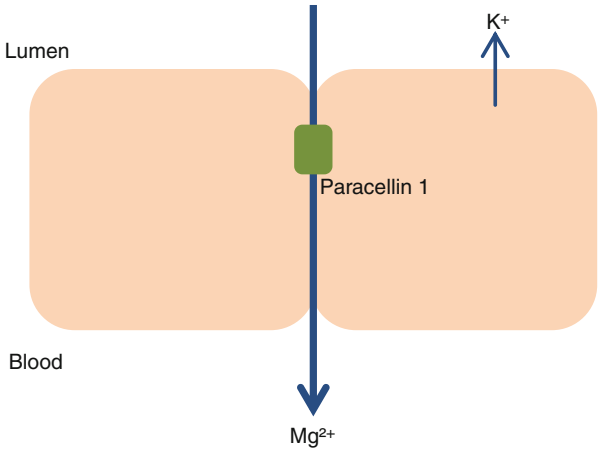

Fig. 13.2 Paracellular pathway

calcium efflux from the sarcoplasmic reticulum [15]. In skeletal muscle, magnesium has been shown to inhibit dihydropyridine receptors to decrease intracellular calcium [15]. The pathway for neurotransmitter release involves phosphorylation of phosphatidylinositol 4,5-bisphosphonate into inositol 1,4,5-triphosphate (IP3), which is subsequently blocked from binding to the IP3-mediated calcium channel by magnesium [5].

13.2.1 Magnesium Absorption and Excretion

Dietary intake of magnesium is estimated to have more than halved in the USA in the last 100 years from approximately 500 to 175–225 mg/day [11] with adolescent females and adult males aged 71 years and over being least likely to have sufficient dietary intake [16]. However, insufficient dietary intake alone is unlikely to result in hypomagnesaemia.

More frequent aetiologies of hypomagnesaemia are increased renal excretion, gastrointestinal losses, decreased gastrointestinal absorption, redistribution or reduced intake with the former two being the most prevalent causes. With regard to normal renal physiology, approximately 80 % total plasma magnesium is filtered through the kidneys of which 3 % is excreted [1, 4, 8, 17]. Reabsorption occurs principally in the cortical segment of the thick ascending limb of the loop of Henle (50–60 %) but the proximal tubule and distal convoluted tubule also have important parts to play, reabsorbing 5–15 and 10 %, respectively [8]. Paracellular magnesium uptake in the cortical thick ascending limb relies on a positive luminal voltage gradient, so the rate of uptake may be altered either by increasing permeability or changing the transepithelial voltage [8]. Negatively charged paracellulin-1 protein has been implicated in this pathway and is expressed in cells in the thick ascending limb of the loop of Henle and the distal convoluted tubule, as shown in Fig. 13.2 [16, 17].

Absorption in the distal convoluted tubule is mediated by transcellular pathways relying on magnesium ion channels MagT1, TRPM6, SLC41A1 and SLC41A2 via

as yet unclear mechanisms [7, 8, 16, 17]. Ca^2/Mg^2 TRPM6 seems to have a significant role, with EGF implicated in the pathway for activation as disabling mutations cause magnesuria [14].

K^+ ions are pumped into the lumen in order to maintain a positive transluminal voltage. This, in combination with the negatively charged paracellin 1 molecule, encourages divalent cations such as Mg^{2+} to be reabsorbed back into the blood.

Gastrointestinal absorption may occur in the entire small intestine and colon [18] but principally magnesium uptake is via the ileum and jejenum [1, 19]. Phytate, fibre and alcohol are several substances that have been shown to reduce magnesium absorption [1, 4, 20]. As with renal absorption, both paracellular and transcellular uptake mechanisms exist, and some studies suggest that although magnesium absorption pathways are distinct from calcium, uptake may be influenced by vitamin D, although this is still debated [4, 17]. Proposed mechanisms for gastrointestinal magnesium absorption include active transport, bulk transport and paracellular uptake [17, 18] but it is not currently understood which mechanisms are predominantly responsibly for magnesium absorption under which conditions.

Magnesium handling is influenced by medications such as diuretics and proton pump inhibitors, alcoholism, diabetes mellitus and hormones such as PTH, glucagon and antidiuretic hormone (ADH) [4, 8].

13.3 Measuring Hypomagnesaemia

It is important to note that patients may be normo-magnesaemic with magnesium deficiency or conversely may be hypomagnesaemic with no physiological magnesium depletion [7, 21]. Measuring serum magnesium has, thus, been debated with regard to its suitability, particularly as a link between serum and intracellular magnesium levels has not been established [4, 21]. Furthermore, there has been much contradictory evidence with regard to the relationship between hypomagnesaemia measured via total serum in critically ill patients and mortality. Some studies conclude that hypomagnesaemia is an effective prognostic indicator [10] while others have found no association [22]. What is certainly not clear is whether the alleged association between hypomagnesaemia and mortality is due to bodily depletion of magnesium.

There are physiological tests available to predict magnesium depletion, such as the magnesium tolerance test. Percentage of retained magnesium is calculated after an infusion, which accurately predicts total body status [4, 7]. Nonetheless, it is reliant upon intact renal excretion, which excludes patients with renal pathologies.

Efforts are being made to find suitable methods for directly measuring ionised magnesium, which is the useful form of magnesium found in the serum. Ionised serum magnesium is usually in the range of 0.54–0.67 mmol/L [4] . However, this has not been easy due to electrode contamination with different cations, particularly calcium. Fluorescent dyes and nuclear magnetic resonance (NMR) spectroscopy are also used in calculating intracellular ionised magnesium but are not routinely available or practical. Currently there are no suitable ways for routinely assessing bodily magnesium status [7, 11, 22].

13.4 Magnesium Deficit: Impact upon the Cardiorespiratory System

There are no pathognomonic ECG abnormalities for hypomagnesaemia but changes seen can include prolonged QT, widened QRS complexes and ST depression. Several cardiac arrhythmias have been linked to hypomagnesaemia of both atrial and ventricular origin, including ventricular tachycardia, atrial tachycardia, atrial fibrillation and torsades de pointes [16].

Indeed magnesium sulphate is a recognised treatment for torsades de pointes irrespective of the patients' serum magnesium levels [5, 23]. Magnesium's effect on arrhythmias has been difficult to study due to the commonly seen concurrent hypokalaemia with hypomagnesaemia. One contributing factor for induction of arrhythmias may be that a decrease in intracellular magnesium subsequently decreases potassium, which affects repolarisation during cardiac action potentials [14]. This may be why magnesium deficit can induce digoxin toxicity, although it may also be due to digoxin's action on the magnesium dependant Na/K-ATPase [5]. At present, however, the exact pathogenesis of arrhythmias in hypomagnesaemia has not been definitively established.

Magnesium has been shown to decrease catecholamine release ex vivo [1] and in rat adrenals [24] and to protect cardiomyocytes from the damaging accumulation of calcium [14], giving it theoretical therapeutic benefits post myocardial infarction (MI). There is some evidence that patients with ischaemic heart disease dying suddenly of acute MI have lower levels of magnesium in cardiac tissue. The LIMIT 2 study showed that administration of magnesium simultaneously with thrombolysis can improve morbidity and decrease the long-term risk of left ventricular failure [25]. However, the much larger ISIS 4 trial contradicted this evidence showing no therapeutic effect of magnesium given after fibrinolysis [26]. The MAGIC trial administered magnesium either simultaneously or before reperfusion techniques and neither trial showed any statistically significant decrease in mortality rates [27]. These studies together seem to show that the role of magnesium in myocardial infarction has been largely succeeded by other medications, namely antiplatelet agents and angiotensin converting enzyme (ACE) inhibitors [16, 26, 27]. However, magnesium deficiency has been epidemiologically linked to development of atherosclerosis, heart failure and hypertension [4]. Although routine use post MI has not been shown to be beneficial it may be that long-term magnesium deficiency predisposes patients to cardiovascular disease and MI.

13.5 Magnesium Deficit: Impact upon the Neurological System

Neurological manifestations of hypomagnesaemia are often the first clinical indications of the electrolyte abnormality. Hypomagnesaemia is known to cause tetany, with positive Chvostek's and Trousseau's signs being found in some patients without concomitant calcium deficiency [28]. Without the competitive inhibition

of magnesium, presynaptic calcium is able to stimulate neurotransmitter release at lower thresholds at neuromuscular junctions. Intracellular calcium is increased due to a combination of release from the sarcoplasmic reticulum coupled with decreased reuptake [7]. Magnesium is frequently used as an anticonvulsant in the treatment of eclampsia, possibly due to these actions. Although there is not currently a role in treatment of epileptic seizures there are other non-eclampsia related seizures for which magnesium therapy may be useful [5, 28]. Vertigo, nystagmus and psychological disturbance may also be features of hypomagnesaemia.

13.6 Treatment of Hypomagnesaemia

Generally, asymptomatic patients with hypomagnesaemia are given oral magnesium supplementation whenever possible. Some patients are unable to tolerate magnesium salts as they often induce nausea. Administration of IV magnesium causes a transient rise in plasma magnesium, leading to increased renal excretion, so it is estimated that approximately 50 % will be wasted [19]. However, haemodynamic instability or symptomatic hypomagnesaemia are both indications for IV magnesium administration.

No clinical trials are currently available regarding optimal magnesium repletion. In the UK, magnesium administration is governed by local hospital guidelines but general guidance is provided below from the British National Formulary alongside Ayuk and Gittoes review article on magnesium homeostasis [7].

It is recommended that magnesium sulphate heptahydrate IV injections for hypomagnesaemia do not exceed 20 % concentration, which may be diluted using 0.9 % sodium chloride or 5 % glucose from 10, 20 and 50 % preparations [7, 23]. The details of these preparations may be seen below in Table 13.2.

Rate and duration of infusion is dependent upon magnesium deficit but should not exceed 2 g/h. In comparison, when prescribing IV magnesium sulphate for pre-eclampsia it is common to give a loading dose of 4 g [29] and in status asthmaticus 2 g over 15–30 min may be prescribed [30]. In the case of torsades de pointes, the BNF recommends 8 mmol (2 g) magnesium sulphate over 10–15 min and to repeat once if necessary [23] .

Up to 160 mmol (40 g) magnesium sulphate over 5 days may be required. Special attention needs to be taken in patients with renal impairment, in whom

Table 13.2 Intravenous magnesium concentration preparation guidance

% solution	Milligrammes magnesium sulphate per mL	Milligrammes elemental magnesium	Mmol/mL
10	100	10	0.4
20	200	20	0.8
50	500	50	2
100	1000	100	4

doses should be lowered with close monitoring of the patients' magnesium level and cardiac function. Intramuscular injection is an alternative to IV administration but is painful. An undiluted 50 % solution of 1–2 g magnesium sulphate may be injected IM every 6 h for up to 24 h [7, 23].

American guidelines recommend treatment of symptomatic hypomagnesaemia with a loading dose of 1–2 g magnesium sulphate in 50–100 mL 5 % dextrose over 5–60 min before setting up an infusion. An infusion of 4–8 g over 12–24 h is recommended and may be repeated as required, bearing in mind that serum magnesium will increase readily upon infusion but correcting intracellular magnesium deficiency can take a few days [7]. Both sets of guidelines aim to maintain plasma concentration above 0.4 mmol/L and recommend patients with renal failure have dosage decreased by 25–50 % [7, 9, 23].

13.7 Complications of Treatment

Excess magnesium supplementation for magnesium repletion can result in hypermagnesaemia. Although this is more likely in patients with impaired renal excretion it is important to look for signs and symptoms of hypermagnesaemia in all patients receiving magnesium therapy. Above concentrations of 2 mmol/L neuromuscular signs often become apparent first [4], followed by cardiovascular, electrolyte and other non-specific symptoms, as summarised in Table 13.3. It is also important to note that hypocalcaemia can exacerbate hypermagnesaemia, causing symptoms at lower concentrations [4].

Less frequent signs are hyperkalaemia in pregnant women, paralytic ileus and alterations in blood clotting.

Discontinuation of magnesium containing therapy and supplements is often sufficient to treat mild hypermagnesaemia. However, further steps may be required beginning with administration of a loop diuretic. Expeditious reversal of symptoms may be achieved by administration of calcium gluconate. In patients with compromised renal function, dialysis is necessary if initial therapies are inadequate [31].

Table 13.3 Symptoms of hypermagnesaemia

	Signs and symptoms		
Magnesium concentration (mmol/L)	Cardiorespiratory	Neuromuscular	Other
2–3	Mild blood pressure drop	Hyporeflexia	Flushing, headache, nausea, drowsiness
3–5	Bradycardia, hypotension, ECG abnormalities; prolonged QT, widened QRS	Complete loss of deep tendon reflexes	Somnolence, hypocalcaemia
>5	Bradycardia, respiratory failure, heart block, cardiac arrest	Flaccid total paralysis	Death

13.8 Further Areas of Research

There are several areas of research that can and are being undertaken in order to better our understanding of magnesium homeostasis and clinical uses. From a cellular perspective, it is currently unclear how magnesium is absorbed; so further work into the precise channels, hormones and overall mechanism at varying magnesium concentrations is required. From a clinical perspective, the aetiology of arrhythmias in hypomagnesaemia is poorly understood, as is whether or not there is any role for magnesium therapy in patients with cardiac arrhythmia, other than torsades de pointes without hypomagnesaemia. Magnesium sulphate in this context may be useful due to an underlying deficiency of magnesium or because of some unknown pharmacology of the drug that is yet to be elucidated [8]. As physicians it would be beneficial to be able to assess intracellular bodily stores of magnesium in an efficient and accurate way. If this in itself is not possible, then a link between one of the current methods for measuring magnesium and prognostic outcome is necessary.

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Transfer of the Sickest Patient in the Hospital: When How and by Whom

14

Michael E. O'Connor and Jonathan M. Handy

14.1 Background

The practice of transferring critically ill patients is common both within and between medical facilities. Accurate figures for the number of such transfers are hard to obtain in the UK as there is currently no national reporting system; nevertheless, available data suggests roughly 4500–11,000 critically ill patients are transferred between hospitals per annum [1, 2].

Transfers may take place for clinical reasons (e.g. for specialist investigation), due to lack of beds in the referring hospital (capacity transfers) or to repatriate the patient to their referring or local hospital.

Since the time of the Napoleonic wars, the transfer of critically ill patients has been shown to be a hazardous process [3]. Despite this knowledge and the publication of comprehensive guidelines [2, 4, 5] adverse incidents are common and have harmful consequences for patients. Surveys from across the world report that a critical incident occurs in 26–34 % of transfers, with one third of incidents being equipment related. Resultant harm to the patient following an incident has been reported in 16.8–59 % of cases [6–9]. Even uneventful transfers are associated with deterioration in gas exchange and increased rates of ventilator-associated pneumonia [10]. For this reason much attention is given to avoiding transfers unless absolutely necessary. Such attention can result in significant reductions in capacity transfers and the associated risks [11].

The use of specialist transfer teams has been shown to reduce the number of critical incidents and adverse outcomes in patients [12]. These results may, in part,

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_14

be explained by the fact that these teams make the 'transfer' the focus of what they do, whereas ad hoc escorting teams are often focused on delivering the patient to the receiving hospital as fast as possible so that they can return to their base hospital.

Specialist teams receive training on the physiological effects of the transfer process, transfer equipment, and solutions to common problems encountered during transfers. The rest of this chapter aims to focus on these areas, but in no way serves as a substitute to 'hands on' training and attending a specialist transfer training course.

14.2 General Principles

Consideration should always be given to the risk of transfer compared with the potential benefits. This risk assessment and the ultimate decision to transfer a critically ill patient should be taken by the consultant in charge of their care. Importantly, whenever and wherever a critically ill patient is transferred the principles remain the same.

14.3 Advanced Planning

There is a popular mantra 'to fail to plan is to plan to fail'; nowhere is this truer than with critical care transfers. Preparation is key to successful transfers and includes advanced planning as well as on-the-day preparation. Long-term planning includes staff training and acquisition of appropriate transfer equipment. Transfer bags are a key component; they should contain only essential equipment. Bag design is crucial as the contents need to be easily identified and accessed in an emergency. Many hospitals use a tag system for sealing bags with a thorough review and replacement of used inventory if the seal is broken. A list of the bag contents and regular checks are essential to this process. Checklists highlighting process and equipment are extremely useful to guide the escorting team performing any transfer, particularly time-critical ones.

Some hospitals utilise standardised documentation which includes a checklist, important information (e.g. contact numbers, oxygen calculations, etc.) and space to document patient vital signs and details of the transfer; such documents improve patient handover (Fig. 14.1).

All transfer equipment should be kept together in a designated area and checked on a daily basis. Service and maintenance schedules should be checked and adhered to. One of the most common incidents to arise during critical care transfers is battery failure; an awareness of this, matched with appropriate maintenance, can significantly reduce such problems [11].

14.4 Immediate Preparation

14.4.1 Communication

Communication breakdown is a common cause for transfer-related incidents and is completely preventable. Communication should start as early as possible and should

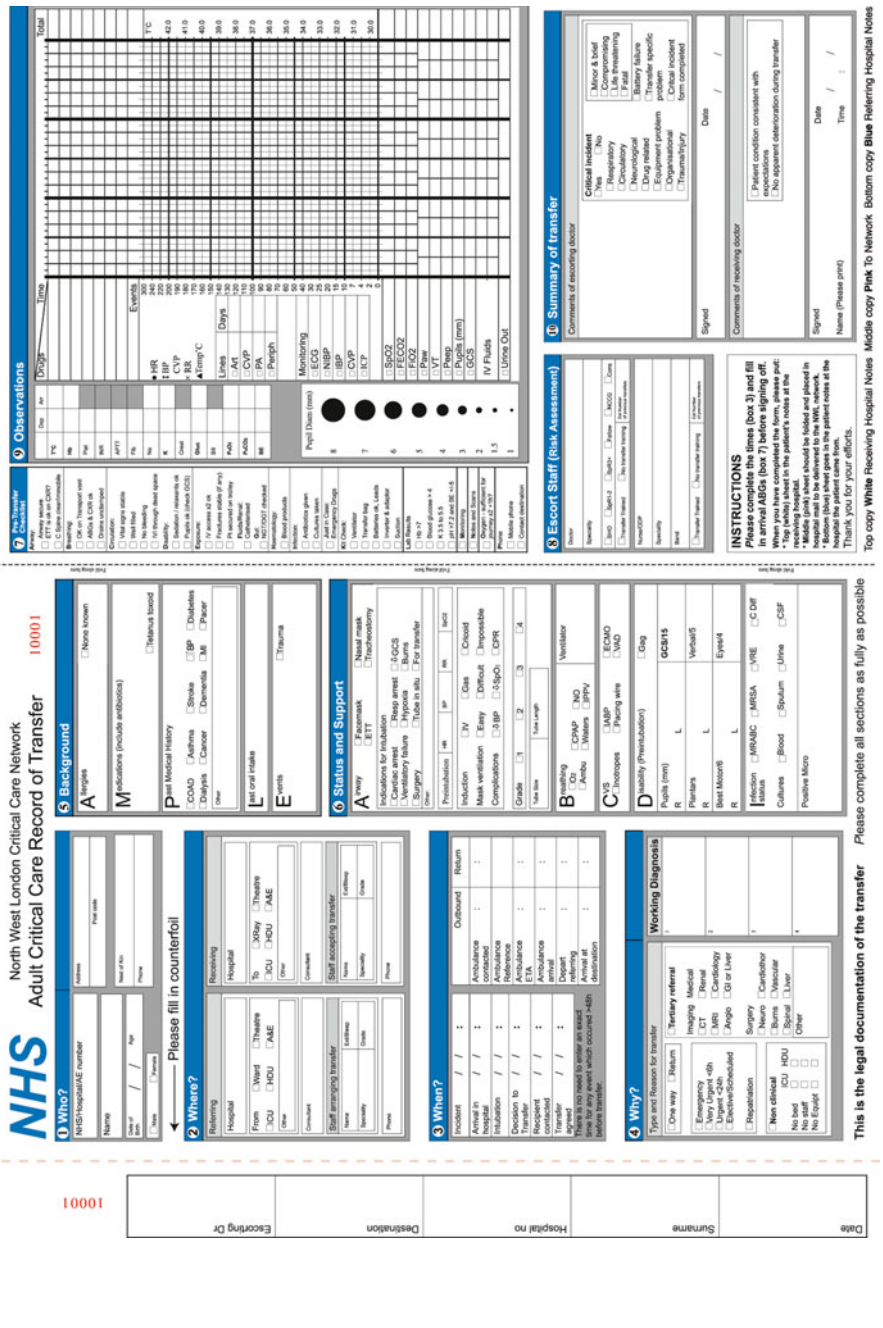

Fig. 14.1 North West Thames Critical Care Network Adult Critical Care Record of Transfer (Reproduced with kind permission of the North West London Critical Care Network)

use closed and targeted terminology in order to avoid misunderstanding. Communication should always start by including senior members of the ICU team.

Once the decision has been made to transfer, this should be discussed with the patient (if feasible) and their relatives as early as possible. The receiving team should be contacted to discuss the patient's history, reason for transfer, their current status and any anticipated problems that may arise before arrival. It is essential that any identified infections and micro-organisms are communicated to the receiving team as the patient may require isolation on arrival. There are myriad examples of multi-resistant organisms spreading due to transferred patients acting as the vector.

Details of the receiving hospital's exact location and contact numbers should be established prior to departure and any specific access routes. Estimated times of departure and arrival should be discussed and further contact should be made if there is significant deviation from these. If any problems or deviations from the plan arise they should be communicated to the receiving team; the latter have an ethical obligation to retain a bed once transfer has been accepted. Once the patient is prepared, on the transfer trolley and in the process of leaving the referring hospital, it is customary for one of the referring ICU team to contact the receiving team to confirm departure.

14.4.2 Who Should Escort the Patient?

The escorting staff should possess the appropriate skills and knowledge to manage the patient for the purposes of the transfer. As a minimum they should have theoretical knowledge of the common problems encountered during transfers and the management required should these problems arise. Ideally, all staff should have undergone training in critical care transfers. In the past, such training has been elusive, but it is increasingly available and can be accessed as free on-line training [13]. Usually, the escorting team will consist of a doctor with airway management skills and a nurse; however, patients may be transferred by any clinical staff provided they have the appropriate training and skills. The composition of the transfer team should be bespoke according to the patient's needs. For the purposes of transferring a patient, the transfer vehicle becomes an extension of the escorting team's usual place of work; as such, their usual employer's insurance and indemnity apply.

14.4.3 Patient Preparation

A detailed system-based review of the patient should be performed during preparation for transfer; time spent stabilising and resuscitating the patient at this point can reduce problems during the transfer and has been shown to reduce length of ICU stay [14].

As part of the patient assessment, the airway must be assessed and secured if necessary. Adequate sedation, analgesia and muscle relaxation must be ensured for patients who are intubated.

As a guide, two large bore and well-secured intravenous cannulae should be in situ prior to transfer. The patient should be appropriately fluid resuscitated with an adequate cardiac output prior to departure; the forces of inertia experienced during acceleration and (more importantly) braking can result in clinically significant intravascular fluid shifts which are exaggerated in hypovolaemic patients. If inotropic agents are required to achieve haemodynamic stability, the patient should be stabilised using these agents prior to departure. Haemodynamic targets should be bespoke to the patient and may need to be significantly lowered for conditions such as ruptured aortic aneurysm (see subspeciality transfer section).

The level of monitoring used during transfer should mirror what is considered essential if the patient were to be managed in the intensive care unit; as a minimum for intubated patients, the following monitoring should be used: ECG, pulse-oximetry and non-invasive blood pressure with the addition of end-tidal CO_2 ($EtCO_2$), inspired oxygen concentration and airway pressure. It is preferable to monitor continuous invasive blood pressure as non-invasive blood pressure can be unreliable and results in greater drain on the monitor's battery. In addition to the above, the patient's temperature should be regularly checked (hypothermia is common during long transfers). Alarm limits and monitor volumes should be checked and amended as necessary.

For transfers that are not time critical, the patient should be established on the transfer monitor and equipment (including the transfer ventilator) for about half an hour before departing. Mains gases and electricity should be used to preserve battery life and portable gas supplies, and an arterial blood gas should be performed to ensure adequate ventilation. Any instability should be resolved before departure; this can result in delays but, if ignored, such deteriorations can result in challenging incidents while in transit.

The duration of transfer should be estimated and used to guide calculations for oxygen, battery and drug requirements. It is prudent to carry 50 % more than these calculated requirements to allow for delays. Where possible, electrical inverters should be used in the transfer vehicle; these convert the AC power supply generated from the vehicle's engine into a DC supply that can be used to power equipment. Drug infusions should be rationalised according to patient requirements and administered via reliable syringe driver pumps; volumetric pumps should not be used during transfers due to the impact of movement artefact on the infusion rates.

A mechanical ventilator is a necessity for all intubated patients and modern transport ventilators are also capable of delivering non-invasive ventilation.

14.4.4 Hazards During Transfer

The main dynamic hazard posed to the patient during transfer is that of acceleration and deceleration. Newton's third law states that 'for every action there is an equal and opposite reaction'. Therefore when the patient is accelerated they will experience an equal and opposite force termed 'inertia'. The most common effect experienced is acceleration towards the patient's head with the resultant inertia causing blood to move towards their feet (N.B. in most countries, patients are loaded into ambulances head first with their head at the front of the ambulance). The reverse

occurs when the patient is accelerated towards their feet (e.g. under heavy braking in an ambulance). In this situation the resultant inertia causes their blood and stomach contents to move towards their head and significant increases in intracranial pressure can occur [15]. A nasogastric or orogastric tube and urinary catheter should be inserted and left on free drainage prior to departure, the former to prevent aspiration of gastric contents as a result of inertial forces.

The exposure of critically ill patients to these forces can lead to significant physiological alterations and pathological consequences [16].

Prevention of instability is best achieved by travelling with an adequately fluid resuscitated patient, in the head-up tilt position, while minimising rapid acceleration and deceleration. It is important to highlight that the same forces will also act elsewhere in the ambulance; all objects (including the transfer personnel) will become ballistics unless secured. If the medical team need to attend to the patient during the transfer, they should inform the driver and wait for approval before removing their safety belt. Failure to wear a safety belt can result in staff not being insured in the event of subsequent injury.

Static hazards posed to the patient and staff include noise, vibration, temperature and atmospheric pressure. Noise hampers communication, can render audible alarms useless and makes the use of a stethoscope impossible. The damaging effects of vibration can be reduced by padding and protecting areas of the patient in contact with hard objects. Exposing the patient to open environments during transfer can result in rapid heat loss and hypothermia.

A static hazard specific to air transfers is the reduction in ambient pressure which leads to expansion of gas filled cavities and relative hypoxia. The hypoxia at altitude, even in a pressurised aircraft cabin must be considered when calculating the oxygen requirements for transfer.

The expansion of closed gas-filled cavities can result in injury and a pneumothorax may expand. Thus it is important to ensure drains are correctly placed and patent prior to take-off; there may be damage to the middle ear if the Eustachian tube is obstructed; and expansion of the gastrointestinal tract may be associated with nausea and vomiting, compromise of venous return or even perforation.

Gas containing equipment will undergo similar expansion when exposed to changes in ambient pressure.

14.5 Diagnostic and Subspecialty Transfers

The following specific transfers follow all of the above principles but with some additional considerations.

14.5.1 Radiology

CT scanning is the most common diagnostic study performed outside of the ICU. High pressure injection of intravenous contrast can lead to extravasation or

damage to multi lumen catheters. Transfer of the patient onto and off the scanning gantry needs to be a well organised process with attention paid not to dislodge items. A check should be performed to ensure that the movement of the gantry does not interfere with the patient or equipment. The monitor should be visible from the control room with audible alarms set. On occasions, a member of the escorting team may need to remain with the patient, in which case appropriate radiation protection should be worn.

The use of MRI for ICU patients is increasing and this poses complex issues. An MRI safety checklist must be filled in by patients and staff. There are specific problems with the function of monitoring systems, ventilators, and infusion pumps caused by the strong magnetic field. The potential for ferrous items to become projectiles means careful planning and high levels of vigilance are required. Depending on the familiarity and availability of equipment it is preferable to use MRI compatible monitoring, infusion pumps and ventilators. Equipment that must be kept some distance from the magnet necessitates long extension tubing, with the adherent risks of disconnection and delayed diagnosis of problems. Discussion with the MRI suite, before the patient is moved, is always advisable.

14.6 Neurosurgical Emergencies

This is a common indication for patient transfer and if performed inadequately can lead to worse patient outcome [7]. The main causes of secondary brain injury such as hypotension, hypoxia, hypercarbia, hyperpyrexia and cardiovascular instability can be minimised by following transfer policies.

There is a balance between sufficient preparation and prompt transfer for surgery. Generally, the ideal physiological parameters to avoid secondary brain injury include adequate oxygen delivery with a PaO_2 greater than 13 kPa, adequate ventilation with a $PaCO_2$ between 4.5–5 kPa [17], and a mean arterial blood pressure greater than 80 mmHg [18]. In addition to the monitoring described previously, pupil size and reaction to light should be checked regularly.

All patients with a GCS of $\leq$8 should be intubated prior to transfer. Intubation should also be performed in all patients who drop their motor score by 2 or more points, and considered in those whose GCS has fallen by 2 or more points regardless of their baseline GCS [19]. Induction of anaesthesia and intubation should take into account the deleterious effects of rises in ICP due to inadequate sedation, analgesia and muscle relaxation. Consideration should also be given to the potential for cervical spine injuries and a full stomach with the associated risk of pulmonary aspiration of gastric contents.

Once intubated, the patient should receive adequate sedation and muscle relaxation while avoiding hypotension and derangements in $PaCO_2$ levels. Hypovolaemic patients are more unstable during transfer [16], and head injured patients tolerate hypotension poorly [18]; therefore, adequate fluid resuscitation should be instituted. Once bleeding has been ruled out or treated, hypotension can be treated with inotropes or vasopressors.

Anticonvulsant drugs can be given as a loading dose prior to transfer if there is a history of seizures, but this is best discussed with the receiving neurosurgical centre [19].

The patient should be positioned with a 30° head-up tilt, central venous lines inserted into the subclavian or femoral veins and tracheal tubes taped in order to aid unobstructed venous return from the head. A steady transfer is preferable to rapid acceleration and deceleration due to the impact of these forces on ICP.

14.7 Vascular Emergencies

Vascular transfers are time critical [20] and the mainstay of preparing these patients for transfer is establishing haemodynamic stability [21]. Guidelines for this are vague, but generally accepted haemodynamic values include a systolic blood pressure of 70–90 mmHg and a heart rate of ≤ 100 bpm; both reduce shear stress across the damaged vessel wall.

Pain should be adequately controlled following which the above parameters may be achieved using a variety of titratable infusions. Cross matching of blood should not delay transfer [22], the blood if available should be taken with the patient to allow urgent use if required.

14.8 Methods of Transfer

14.8.1 Road Ambulances

These are the most efficient means of transporting patients over short distances. Ideally a road transfer should involve steady driving and blue lights and sirens to clear the traffic. The advantage of using a road ambulance is door-to-door service. It is easier to train personnel and divert to the nearest hospital if the patient deteriorates en route. They can however be uncomfortable, nauseating, and cramped.

14.8.2 Fixed Wing

Aeroplanes have the advantage of speed and reach. They can be very cramped environments with limited access to the patient, and, of course, they necessitate a road transfer at each end of the journey. There is little margin for error in terms of missing or faulty equipment or a decline in the patient's condition. In addition to the common transfer problems of vibration, acceleration forces, noise and temperature, the effects of turbulence and altitude need to be considered in terms of the impact on patient physiology.

14.8.3 Helicopters

Helicopters have the advantage of reducing transfer times with the ability to land close to incidents, and deliver pre-hospital care teams to trauma victims in high traffic density areas. They are a practical way to perform secondary transfers if hospitals have a helipad. Helicopters can achieve a smoother transfer than road ambulances with less acceleration and deceleration once airborne. Helicopters typically fly at lower altitudes than planes avoiding problems from low ambient pressure. Helicopters are, however, noisy and cramped, suffer from large amounts of vibration, and are limited by weather conditions.

14.9 Summary

Whatever form and distance taken during the transfer of a critically ill patient, the same principles apply. There is no substitute for advanced planning and meticulous preparation. Transfer training is increasingly available and is recommended for all escorting personnel. Awareness of potential risks and planning for the appropriate responses goes a long way to preventing incidents and improving their outcome when they do occur.

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Erratum to Contributors and Chapter 3 in Key Topics in Management of the Critically Ill

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Erratum to Contributors
DOI: 10.1007/978-3-319-22377-3

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Erratum to Chapter 3:

M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_3

The affiliation of the author Ian Conrick-Martin on the chapter opening page of chapter 3 was incorrect.

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The online version of the original chapter can be found under
DOI:10.1007/978-3-319-22377-3_3

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M.P. Vizcaychipi, C.M. Corredor (eds.), *Key Topics in Management of the Critically Ill*,
DOI 10.1007/978-3-319-22377-3_15